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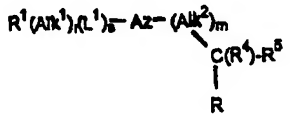

(1)

(57) Abstract

Aromatic amines of formula (1) are described: wherein Az is an optionally substituted monocyclic six–membered nitrogen–containing aromatic group; L^1 is a linker atom or group; R is a carboxylic acid or a derivative thereof; and R^5 is a group $-L^2(CH_2)_iR^6$ in which L^2 is a $-N(R^7)CO-$ or $-N(R^7)CS-$ group. The compounds are able to inhibit the binding of α_4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

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AROMATIC AMINE DERIVATIVES AS PHARMACEUTICAL AGENTS

This invention relates to a series of aromatic amine derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T A. Nature, 346, 425, (1990); Springer, T. A. Cell 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. Current Topics in Microbiology and Immunology, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha 4\beta 1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. *et al* J. Exp. Med. 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al* Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al* J. Immunol. 157, 4094, (1996)]. A number of monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

One particular integrin subgroup of interest involves the α4 chain which can pair with two different beta chains β1 and β7 [Sonnenberg, A. *ibid*]. The α4β1 pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. α4β1 binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between α4β1 and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

The integrin generated by the pairing of α4 and β7 has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like α4β1, binds to VCAM-1 and fibronectin. In addition, α4β7 binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between α4β7 and MAdCAM-1 may also be important at

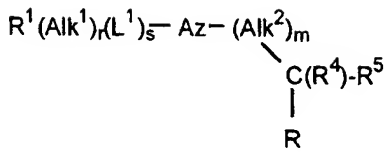
sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised by α4β1 and α4β7 when they bind to their ligands have been identified. α4β1 seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst α4β7 recognises a LDT sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N. Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol. 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the α4β1 binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes inhibition of their ligand binding functions can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is very important to be able to identify selective inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of the binding of α4 integrins to their ligands. Members of the group are able to inhibit the binding of α4 integrins such as α4β1 and/or α4β7 to their ligands at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

Thus according to one aspect of the invention we provide a compound of formula (1)



(1)

wherein

Az is an optionally substituted monocyclic six-membered nitrogen-containing aromatic group;

R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a linker atom or group;

r and s is each zero or an integer 1;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^4 is a hydrogen atom or a methyl group;

R^5 is a group $-L^2(CH_2)_tR^6$ in which L^2 is a $-N(R^7)CO-$ [where R^7 is a hydrogen atom or a straight or branched alkyl group] or $-N(R^7)CS-$ group, t is zero or the integer 1, and R^6 is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

R is a carboxylic acid ($-CO_2H$) or a derivative thereof;

and the salts, solvates and hydrates thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diasteromers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

Six-membered nitrogen-containing aromatic groups represented by the group Az in compounds of the invention include pyridyl, pyrimidinyl,

pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl and 1,2,3-triazinyl groups. Generally, each of said groups may be linked to the remainder of the compound of formula (1) through any available carbon atom in the ring represented by Az. Where desired, one or two additional substituents may be present on each Az group, for example one or two halogen atoms and/or straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro groups.

When the optional substituent on Az is an alkyl group it may be for example a straight or branched C_{1-6}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group. Alkoxy groups optionally present on Az include straight or branched C_{1-6}alkoxy groups such as methoxy or ethoxy groups. Halogen atoms include for example fluorine, chlorine, bromine or iodine atoms. When the optional substituent on Az is a haloalkyl or haloalkoxy group it may be for example a haloC_{1-6}alkyl or haloC_{1-6}alkoxy group containing one, two or three halogen atoms selected from fluorine, chlorine, bromine or iodine atoms. Particular examples of groups of this type include $-CF_3$, $-OCF_3$, $-CCl_3$, $-OCCl_3$, $-CHF_2$, $-OCHF_2$, $-CHCl_2$, $-OCHCl_2$, $-CH_2F$, $-OCH_2F$, $-CH_2Cl$ and $-OCH_2Cl$ groups.

In the compounds of formula (1), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters and amides include those $-CO_2Alk^5$, $-CONH_2$, $-CONHR^{12}$ and $-CON[R^{12}]_2$ groups described below in relation to the group R^6.

Alk^2 in the compounds of the invention may be for example a straight or branched C_{1-3}alkylene chain. Particular examples include $-CH_2-$, $-CH(CH_3)-$ and $-(CH_2)_2-$.

When in the compounds of the invention L^1 is present as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$ [where R^8 is a hydrogen atom or an optionally substituted straight or branched alkyl group], $-CON(R^8)-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CSN(R^8)-$, or

-$N(R^8)SO_2N(R^8)$- groups. Where the linker group contains two R^8 substituents, these may be the same or different.

When Alk^1 and/or R^6 in compounds of formula (1) is an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene chains.

Heteroaliphatic chains represented by Alk^1 and/or R^6 include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^3 where L^3 is as defined above for L^1 when L^1 is a linker atom or group. Each L^3 atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to an adjoining atom or group.

Particular examples of aliphatic chains represented by Alk^1 and R^6 include optionally substituted -CH_2-, -CH_2CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -$(CH_2)_2CH_2$-, -$CH(CH_3)CH_2$-, -$(CH_2)_3CH_2$-, -$CH(CH_3)CH_2CH_2$-, -$CH_2CH(CH_3)CH_2$-, -$C(CH_3)_2CH_2$-, -$(CH_2)_4CH_2$-, -$(CH_2)_5CH_2$-, -CHCH-, -$CHCHCH_2$-, -CH_2CHCH-, -$CHCHCH_2CH_2$-, -$CH_2CHCHCH_2$-, -$(CH_2)_2CHCH$-, -CC-, -$CCCH_2$-, -CH_2CC-, -$CCCH_2CH_2$-, -CH_2CCCH_2-, or -$(CH_2)_2CC$- chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L^3 to form an optionally substituted heteroaliphatic chain. Particular examples include optionally substituted -L^3CH_2-, -$CH_2L^3CH_2$-, -$L^3(CH_2)_2$-, -$CH_2L^3(CH_2)_2$-, -$(CH_2)_2L^3CH_2$-, -$L^3(CH_2)_3$- and -$(CH_2)_2L^3(CH_2)_2$- chains.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 and R^6 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include -NHR^9 and -$N(R^9)_2$ groups where R^9 is

a straight or branched alkyl group. Where two R^9 groups are present these may be the same or different. Particular examples of substituted chains represented by Alk^1 include those specific chains just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example chains of the type $-CH(CF_3)-$, $-C(CF_3)_2-$ $-CH_2CH(CF_3)-$, $-CH_2C(CF_3)_2-$, $-CH(CF_3)-$ and $-C(CF_3)_2CH_2$.

Optionally substituted cycloaliphatic groups represented by R^1 and/or R^6 in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g C_{3-7} cycloalkenylgroups.

Optionally substituted heterocycloaliphatic groups represented by R^1 and/or R^6 include optionally substituted C_{3-10}heterocycloaliphatic groups. Particular examples include optionally substituted C_{3-10}heterocycloalkyl, e.g. C_{3-7} heterocycloalkyl, or C_{3-10}heterocycloalkenyl, e.g. C_{3-7} heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L^3 as just defined.

Optionally substituted polycycloaliphatic groups represented by R^1 and/or R^6 include optionally substitued C_{7-10} bi- or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted polyheterocycloaliphatic groups represented by R^1 and/or R^6 include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^3 atoms or groups.

Particular examples of R^1 and R^7 .cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl,

thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the R^1 and R^6 cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or polyheterocycloaliphatic groups include one, two, three or more substituents each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, or $-(Alk)_vR^9$ groups in which Alk is a straight or branched C_{1-3}alkylene chain, v is zero or an integer 1 and R^9 is a -OH, -SH, $-N(R^{8a})_2$, -CN, $-CO_2R^{8a}$, $-NO_2$, $-CON(R^{8a})_2$, $-CSN(R^{8a})_2$, $-COR^{8a}$, $-CSN(R^{8a})_2$, $-N(R^{8a})COR^{8a}$, $-N(R^{8a})CSR^{8a}$, $-SO_2N(R^{8a})_2$, $-N(R^{8a})SO_2R^{8a}$, $-N(R^{8a})CON(R^{8a})_2$, $-N(R^{8a})CSN(R^{8a})$ or $-N(R^{8a})SO_2N(R^{8a})_2$ group in which R^{8a} is an atom or group as defined herein for R^8. Additionally, when R^6 is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^4)_p(Alk^3)_qR^{10}$ in which L^4 is $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-S(O)_2-$, $-CON(R^8)-$, $-CSN(R^8)-$, $-SON(R^8)-$ or $SO_2N(R^8)-$; p is zero or an integer 1; Alk^3 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R^{10} is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk^3 include those optionally substituted chains described above for Alk^1.

Cycloaliphatic, heterocycloaliphatic, polycyloaliphatic or polyheterocycloaliphatic groups represented by R^{10} include those groups just described for R^1 and R^6. Optional substituents which may be present on these

groups include those described above in relation to Alk^1 aliphatic and heteroaliphatic chains.

Optionally substituted aromatic or heteroaromatic groups represented by R^{10} include those aromatic and heteroaromatic groups generally and specifically described below for R^1 and/or R^6.

In the compounds of formula (1), optionally substituted aromatic groups represented by the groups R^1, R^6 and/or R^{10} include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups .

Optionally substituted heteroaromatic groups, represented by the groups R^1, R^6 and/or R^{10} in compounds of formula (1) include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl,

pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by R^1 include one, two, three or more of the substituents just described for R^1 cycloaliphatic groups.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by R^1, R^6 and/or R^{10} include one, two, three or more substituents, each selected from an atom or group R^{11} in which R^{11} is $-R^{11a}$ or $-Alk^4(R^{11a})_m$, where R^{11a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{12}$ [where R^{12} is an $-Alk^4(R^{11a})_m$, aryl or heteroaryl group], $-CSR^{12}$, $-SO_3H$, $-SO_2R^{12}$, $-SO_2NH_2$, $-SO_2NHR^{12}$ $SO_2N(R^{12})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{12}$, $-CSNHR^{12}$, $-CON[R^{12}]_2$, $-CSN(R^{12})_2$, $-N(R^8)SO_2R^{12}$, $-N(SO_2R^{12})_2$, $-N(R^8)SO_2NH_2$, $-N(R^8)SO_2NHR^{12}$, $-N(R^8)SO_2N(R^{12})_2$, $-N(R^8)COR^{12}$, $-N(R^8)CON(R^{12})_2$, $-N(R^8)CSN(R^{12})_2$, $-N(R^8)CSR^{12}$, $-N(R^8)C(O)OR^{12}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other -O- or -S- atoms or $-N(R^8)-$, -C(O)- or -C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^8)SO_2NHet^1$, $-N(R^8)CONHet^1$, $-N(R^8)CSNHet^1$, $-SO_2N(R^8)Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^8)-$, -C(O)- or -C(S)- groups], $-CON(R^8)Het^2$, $-CSN(R^8)Het^2$, $-N(R^8)CON(R^8)Het^2$, $-N(R^8)CSN(R^8)Het^2$, aryl or heteroaryl group; Alk^4 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ [where n is an integer 1 or 2] or $-N(R^{13})-$ groups [where R^{13} is a hydrogen atom or C_{1-6}alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^8 or R^{12} groups are present in one of the above substituents, the R^8 or R^{12} groups may be the same or different.

When in the group $-Alk^4(R^{11a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{11a} may be present on

any suitable carbon atom in -Alk^4. Where more than one R^{11a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk^4. Clearly, when m is zero and no substituent R^{11a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^4 becomes an alkyl, alkenyl or alkynyl group.

When R^{11a} is a substituted amino group it may be for example a group -NHR^{12} [where R^{12} is as defined above] or a group -N(R^{12})$_2$ wherein each R^{12} group is the same or different.

When R^{11a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{11a} is a substituted hydroxyl or substituted thiol group it may be for example a group -OR^{12} or a -SR^{12} or -SC(=NH)NH$_2$ group respectively.

Esterified carboxyl groups represented by the group R^{11a} include groups of formula -CO_2Alk^5 wherein Alk^5 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^5 group include R^{11a} substituents described above.

When Alk^4 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene

chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)$_2$- or -N(R^8)- groups.

Aryl or heteroaryl groups represented by the groups R^{11a} or R^{12} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group R^6. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When -NHet^1 or -Het^2 forms part of a substituent R^{11} each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet^1 or -Het^2 include those substituents described above in relation to Alk^1 chains.

Particularly useful atoms or groups represented by R^{11} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrrolyl, furyl, thiazolyl, or thienyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino (-NH_2), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, imido, such as

phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO_2H), -CO_2Alk^6 [where Alk^6 is as defined above], C_{1-6} alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH_2, sulphonyl (-SO_3H), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH_2, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonyl-amino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy,

benzyloxycarbonylamino, benzyloxycarbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{11} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{11} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R^1, R^6 and/or R^{10}.

Straight or branched alkyl groups represented by R^7, R^8 and/or R^9 in compounds of the invention include straight or branched C_{1-6}alkyl e.g. C_{1-3}alkyl groups such as methyl or ethyl groups. Each R^8 group may be optionally substituted, for example by one or more atoms or groups of the types described previously as optional Alk^1 substituents.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

Generally in the compounds of the invention the group R is preferably a $-CO_2H$ group.

Alk^2 in compounds of formula (1) is preferably a $-CH_2-$ chain and m is preferably an integer 1.

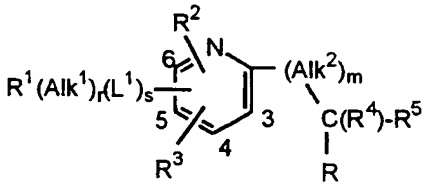
R^4 in compounds of the invention is preferably a hydrogen atom.

In general in compounds of formula (1) $-(Alk^1)_r(L^1)_s-$ is preferably $-CH_2O-$, $-S(O)_2O-$ or $-CON(R^8)-$, particularly -CONH-.

The group R^1 in compounds of formula (1) is preferably an optionally substituted aromatic or heteroaromatic group. Particularly useful groups of these types include optionally substitued phenyl, pyridyl or pyrimidinyl groups. Particularly useful substituents include one or two R^{11} atoms or groups as generally or particularly described herein. Especially useful substituents of this type include one or two halogen atoms or alkyl, alkoxy, haloalkyl, or haloalkoxy groups as described herein.

The group Az in the compounds according to the invention may in particular be an optionally substituted pyridyl group.

Thus, one particular class of compounds of the invention may have the formula (1a):



(1a)

where R^1, Alk^1, r, L^1, s, Alk^2, m, R, R^4 and R^5 are as defined for formula (1) and R^2 and R^3, which may be the same or different, is each a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group; and the salts, solvates and hydrates thereof.

Particular halogen atoms, alkyl, haloalkyl, alkoxy or haloalkoxy groups represented by R^2 and/or R^3 include those atoms and groups described previously in relation to optional Az substituents.

One particular class of compounds of formula (1a) is that wherein the $R^1(Alk^1)_r(L^1)_s$ group is present at the 5-position of the pyridyl ring as shown.

Particularly useful classes of compounds of formula (1) and (1a) are those wherein R^5 is a $-NHCOR^6$ or $-NHCSR^6$ group.

In general in compounds according to the invention R^6 may especially be an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted C_{5-7}heterocycloaliphatic, especially optionally substituted pyrrolidinyl or thiazolidinyl, optionally substituted phenyl and optionally substituted C_{5-7}heteroaromatic, especially optionally substituted pyridyl groups. Optional substituents on these groups include in particular R^{11} atoms or groups where the group is an aromatic or heteroaromatic group and $-(L^4)_p(Alk^3)_qR^{10}$ groups as described earlier where the group is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl or thiazolidinyl group. Particularly useful $-(L^4)_p(Alk^3)_qR^{10}$ groups include those in which L^3 is a -CO- group. Alk^3 in these groups is preferably present (i.e. q is preferably an integer 1) and in particular is a $-CH_2$-chain. Compounds of this type in which R^{10} is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, pyridyl or imidazolyl group are particularly preferred.

Particularly useful compounds according to the invention are:

N-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-[5-(2,6-dichlorobenzyloxy)-pyrid-2-y]propanoic acid;
N-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propanoic acid;
2-[*N*-(2-Chloropyrid-3-oyl)-amino]-3-[*N'*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionic acid;
and the salts, solvates and hydrates thereof

Compounds according to the invention are potent and selective inhibitors of the binding of $\alpha 4$ integrins to their ligands. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role. The invention extends to such uses and to the use of the compounds for preparing a medicament for treating these diseases and disorders. Particular diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as

binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

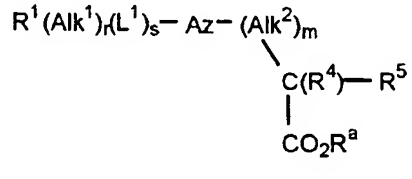
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R, R^1-R^5, L^1, Az, Alk^1, Alk^2, m, r and s when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention

described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-CO_2H$ group may be obtained by hydrolysis of an ester of formula (2):

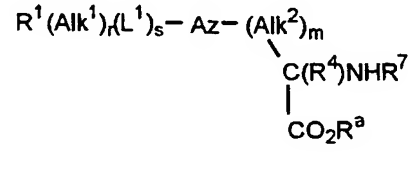


(2)

where R^a is an alkyl group, for example a C_{1-6}alkyl group such as a methyl or ethyl group.

The hydrolysis may be performed using either an acid or a base depending on the nature of R^a, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium hydroxide optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of such solvents may be used.

Esters of formula (2) in which R^5 is a $-N(R^7)CO(CH_2)_tR^6$ group may be prepared by coupling an amine of formula (3):



(3)

or a salt thereof with an acid $R^6(CH_2)_tCO_2H$ or an active derivative thereof. Active derivatives of acids include anhydrides, esters and halides.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around -30°C to around ambient temperature, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine, pyridine, or dimethyl-aminopyridine, or a cyclic amine, such as N-methylmorpholine.

Where an acid $R^6(CH_2)_tCO_2H$ is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclo-hexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxy-benzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the amine of formula (2).

Esters of formula (2) in which R^5 is a $-N(R^7)CS(CH_2)_tR^6$ groups may be preapred by treating a corrsponding ester in which R^5 is a $-N(R^7)CO(CH_2)_tR^6$ group with a thiation reagent, such as Lawesson's Reagent, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

This reaction may not be particularly suitable with starting materials in which other carbonyl groups are present, for example in L^1 and/or R^6, and which might undesirably participate in the reaction. To avoid this the reaction with the thiation reagent may be performed earlier in the synthesis of the compound of the invention with an intermediate in which other carbonyl groups are absent and any required carbonyl groups then subsequently introduced by for example acylation as generally described hereinafter.

The amines of formula (3) may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1) and (2) where appropriate functional groups exist in these compounds. Additionally, although many of the acid intermediates $R^6(CH_2)_tCO_2H$ for use in the coupling reaction described above are known, other desired acids can be derived therefrom using these standard synthetic methods.

Thus, for example compounds of formulae (1), (2) and (3) and acids $R^6(CH_2)_tCO_2H$ may be prepared by alkylation, arylation or heteroarylation. In one example compounds containing a L^1H or L^4H group may be alkylated or arylated using a reagent $R^1(Alk^1)_rX$, or $R^{10}(Alk^3)_qX$ in which X is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The alkylation or arylation reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In a second example, intermediate amines of formula (3) may be prepared by alkylation of a glycinate, for example N-(diphenylmethylene)glycinate with a halide $R^1(Alk^1)_r(L^1)_sAzCH_2Hal$ (where Hal is a halogen atom such as a bromine or iodine atom) in the presence of a strong base, for example a hindered, non-nucleophilic base such as lithium diisopropylamide in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran at a low temperature e.g. around -70°C. The intermediate halide starting

materials for this process are either known compounds or may be prepared from readily available compounds using methods analogous to the preparation of the known starting materials [see for example Myers, A.G. and Gleason, J.L., J.Org. Chem (1996), 61, 813-815].

In another example, compounds of formulae (1), (2) and (3) containing a L^1H group (where L^1 is for example a -NH- group) and acids $R^6(CH_2)_tCO_2H$ may be functionalised by acylation or thioacylation, for example by reaction with a reagent $R^1(Alk^1)_rL^1X$, [wherein L^1 is a -C(O)-, -C(S)-, $-N(R^8)C(O)$ or $-N(R^8)C(S)-$ group], $R^{10}(Alk^3)_qCOX$ or $R^{10}(Alk^3)_qNHCOX$ in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethyl-formamide, at for example ambient temperature, or by reaction with $R^1(Alk^1)_rCO_2H$ or $R^{10}(Alk^3)_qCO_2H$ or an activated derivative thereof, for example as described above for the preparation of esters of formula (2).

In a further example a compound may be obtained by sulphonylation of a compound where $R^1(Alk^1)_r(L^1)_s$ is an -OH group by reaction with a reagent $R^1(Alk^1)_rL^1Hal$ [in which L^1 is -S(O)- or $-SO_2-$ and Hal is a halogen atom such as a chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, a compound where $R^1(Alk^1)_r(L^1)_s$ is a $-L^1H$ group, may be coupled with a reagent R^1OH (where R^1 is other than a hydrogen atom) or R^1Alk^1OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate to yield a compound containing a $R^1(Alk^1)_rO-$ group.

In a further example, ester groups $-CO_2Alk^5$ in the compounds may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed

hydrolysis depending on the nature of the group Alk^5 using the reactants and conditions described above for the hydrolysis of esters of formula (2).

In another example, $-OR^{12}$ groups [where R^{12} represents an alkyl group such as methyl group] in compounds of formulae (1) or (2) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{12}$ group (where R^{12} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [$-CO_2Alk^5$] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups in compounds of formulae (1) or (2) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO_2] group may be reduced to an amine [-NH_2], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L^1 or L^3 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suit able solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

The following Examples illustrate the invention. All temperatures are in °C. All ^{1}Hnmr data is at 300mHz and at 300°K unless otherwise stated. The following abbreviations are used:

EDC - 1-(3-dimethylaminopropyl)3-ethycarbodiimide;
DMF - dimethylformamide; DMSO - dimethylsulphoxide;
HOBT - 1-hydroxybenzotriazole; THF - tetrahydrofuran;
DCM - dichloromethane; MeOH - methanol;
LDA - lithium diisopropylamide EtOAc - ethyl acetate;
NMM - N-methylmorpholine; EtOH - ethanol;
pyr - pyridine; Ar - aryl;
Me - methyl; thiopro - thioproline;
Et_2O - diethyl ether

INTERMEDIATE 1

Ethyl N-(diphenylmethylene)-2-amino-3-(5-benzenesulphonyloxy-pyrid-2-yl)propionate

A solution of ethyl *N*-(diphenylmethylene)glycinate (1.71g, 6.40mmol) in dry THF (10ml) was added to a stirred solution of LDA (2M in heptane/ THF/ethylbenzene, 3.20ml, 6.40mmol) in dry THF (10ml) at -70° under

nitrogen. After stirring at this temperature for 0.75h, a solution of 5-benzenesulphonyloxy-2-bromomethyl-pyridine [2.00g, 6.01mmol; prepared as described by Myers *et al*, J.Org.Chem. (1996), 61, 813] in dry THF (10ml) was added. The reaction mixture was stirred at -70° for 1h then at room temperature for 18h. The reaction was quenched with water (10ml) then partitioned between EtOAc (70ml) and brine (30ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 40ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford the crude proudct as a dark oil. Purification by flash chromatography (silica, 60% to 75% Et_2O/ hexane; applied as DCM solution) afforded the title compound as a tan-coloured solid (2.25g, 72%). δH ($CDCl_3$) 8.02 (1H, d, J 2.8Hz, pyr-H(6), 7.72 (2H, d, J ~8Hz, ortho-Ar-H), 7.59 (1H, t, J ~8Hz, para-Ar-H), 7.50 (2H, dd, J 8.4, 1.4Hz, phenyl-H), 7.40-7.27 (8H, ms, Ar and phenyl-H), 7.19 (1H, dd, J 8.5, 2.8Hz, pyr-H(4), 7.11 (1H, d, J 8.5Hz, pyr-H(3), 6.67 (2H, br d, J ~8Hz, phenyl-H), 4.50 (1H, dd, J 9, 4.6Hz, CH-α), 4.24-4.10 (2H, sym.m. CH_2CH_3), 3.50-3.33 (2H, m, pyr-CH_2), 1.24 (3H, t, J 7.2Hz, CH_2CH_3); m/z (ESI) 515 (MH^+).

INTERMEDIATE 2

Ethyl 2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propionate

A solution of Intermediate 1 (1.9g, 3.7mmol) in 10% aqueous HCl (5ml) and ethanol (120ml) was stirred at room temperature for 1.5h. Most of the solvent was removed *in vacuo* and the residue partitioned between half-saturated aqueous $NaHCO_3$ (50ml) and EtOAc (80ml). The phases were separated and the aqueous layer re-extracted with EtOAc (4 x 40ml) and evaporated *in vacuo*. The obtained yellow oil was chromatographed (silica; EtOAc) to afford the title compound as a colourless oil (1.15g, 78%). δH ($CDCl_3$) 8.04 (1H, d, J 2.8Hz, pyr-H(6)), 7.80 (2H, d, J ~8Hz, ortho-Ar-H), 7.65 (1H, t, J ~8Hz, para-Ar-H), 7.51 (2H, t, J ~8Hz, meta-Ar-H), 7.31 (1H, dd, J 8.5, 2.8Hz, pyr-H(3)), 7.12 (1H, dd, J 8.5Hz, pyr-H(3)), 4.10 (2H, q, J 7.1Hz, CH_2CH_3), 3.86 (1H, dd, J 7.9, 4.9Hz, CH-α), 3.19 (1H, dd, J 14.4, 4.9Hz, pyr-CH_AH_B), 2.99 (1H, dd, J 14.4, 7.9Hz, pyr-CH_AH_B), 1.66 (2H, br s, NH_2), 1.17 (3H, t, J 7.1Hz, CH_2CH_3); m/z (ESI) 351 (MH^+).

INTERMEDIATE 3

Ethyl *N, N*-Di-(2,6-dichlorobenzoyl)-6-amino-pyridine-3-carboxylate

2,6-Dichlorobenzoylchloride (7.5g, 5.2ml, 26.1mmol) was added to a stirred slution of ethyl 6-aminonicotinate (4.0g, 24.1mmol) and NMM (3.65g, 3.97ml, 36.13mmol) in dry DCM (60ml) and stirred at room temperature for 5 days. The phases were separated and the aqueous layer re-extracted with DCM (2 x 50ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (40ml) and brine (20ml), dried ($MgSO_4$) and evaporated *in vacuo* to afford the crude product as a mixture of the mono-benzoylated and di-benzoylated products. Chromatography (silica; 0.5—>1.5% EtOH/DCM) afforded the less polar title compound as a pale yellow viscous oil (6.3g, 51%). δH ($CDCl_3$) 8.97 (1H, d, with fine coupling), 8.31 (1H, d, J 8.2Hz with fine coupling), 7.72 (1H, d, J 8.2Hz), 7.40-7.00 (6H, broad symmetric peak), 4.37 (2H, q, J 7.2Hz) and 1.37 (3H, t, J 7.2Hz); m/z (ESI, 60V), 511 (MH^+).

INTERMEDIATE 4

***N,N*-Di-(2,6-Dichlorobenzoyl)-6-amino-3-(hydroxymethyl)pyridine**

Lithium aluminium hydride (1M in THF, 5.66ml, 22.54mmol of hydride) was added dropwise to a stirred ice-bath cooled solution of Intermediate 3 (5.25g, 10.54mmol) in dry THF (60ml) and stirred under nitrogen for 1h. The reaction was quenched withEtOAc (5ml) and partitioned between 10% aqueous NH_4Cl (60ml) and EtOAc (100ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 50ml). The combined organic extracts were washed with brine (20ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained yellow foam was chromatographed (silica; 2—>4% MeOH/DCM) affording the title compound as a white foam (4.98g). δH ($CDCl_3$) 8.32 (1H, d, J 2.3Hz), 7.71 (1H, dd, J 8.1, 2.3Hz), 7.62 (1H, d, J 8.1Hz), 7.50-6.95 (6H, broad peak), 4.63 (2H, d, J 5.3Hz) and 2.09 (1H, J 5.7Hz); m/z (ESI, 60V), 469 (MH^+).

INTERMEDIATE 5

***N,N*-(Dichlorobenzoyl)-6-amino-3-chloromethyl-pyridine**

Hydrogen chloride gas was bubbled through a stirred solution of Intermediate 4 (2.5g, 5.30mmol) in dry DCM (50ml) for 15 seconds. Thionyl chloride (525µl, 858mg, 7.21mmol) was added and the reaction

stirred for 2h at room temperature. The volatiles were removed *in vacuo* and the residue partitioned between saturated aqueous $NaHCO_3$ (40ml) and DCM (75ml). The phases were separated and the aqueous layer re-extracted with DCM (2 x 20ml). The combined organic extracts were washed with brine (15ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a white foam (2.33g, 90%) δH ($CDCl_3$) 8.37 (1H, d, J 2.3Hz), 7.75 (1H, dd, J 8.2, 2.3Hz), 7.64 (1H, d, J 8.2Hz), 7.48-6.92 (6H, broad peak) and 4.49 (2H, s). m/z (ESI, 60V), 487 (MH^+).

INTERMEDIATE 6

Ethyl *N*-(diphenylmethylene)-2-amino-3-[*N'*,*N*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionate

LDA (2M in heptane/THF/ethylbenzene, 2.59ml, 5.18mmol) was added to a stirred solution of ethyl (N-diphenylmethylene)glycinate (1.32g, 4.94mmol) in dry THF (20ml) at -70° and stirred at this temperature under N_2 for 0.75h. A solution of Intermediate 5 (2.30g, 4.70mmol) in dry THF (20ml) was added, and the reaction mixture stirred at -70° for 0.5h and at room temperature for 6h. The reaction was partitioned between EtOAc (60ml) and water (40ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford a dull yellow oil. Chromatography (silica; 50% Et_2O/hexane; applied in DCM) afforded the title compound as a pale yellow foam (1.47g, 41%) δH ($CDCl_3$) 8.16 (1H, d, J 1.9Hz), 7.56-6.50 (18H, various m's), 4.16 (1H, obscured m), 4.15 (2H, q, J 7.1Hz) and 1.25 (3H, t, J 7.1Hz); m/z (ESI), 60V) 718 (MH^+).

INTERMEDIATE 7

Ethyl-2-amino-3-[*N*,*N*-dichlorobenzoyl)-6-amino-pyrid-3-yl]propionate

A solution of Intermediate 6 (1.40g) and ethanol (50ml) was stirred at room temperature for 1h. The volume of reaction mixture was reduced *in vacuo* by about half neutralized with solid $NaHCO_3$, then evaporated *in vacuo* to near dryness. The residue was partitioned between EtOAc(70ml) and water (40ml), the phases separated and the aqueous layer re-extracted with EtOAc (2 x 40ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* The obtained

yellow oil was chromatographed (silica; 3% MeOH/DCM) to afford the title compound as a white foam (0.87g, 81%). δH ($CDCl_3$) 8.23 (1H, s), 7.57 (1H s), 7.56 (1H, s), 7.48-6.92 (6H, broad peak), 4.11 (2H, q, J 7.1Hz), 3.60 (1H, dd, J 7.4, 5.6Hz), 2.96 (1H, dd, J 13.8, 5.6 Hz), 2.81 (1H, dd, J 13.8, 7.4Hz), 1.31 (2H, br s) and 1.23 (3H, J 7.1HZ); m/z (ESI, 60V) 554 (MH^+).

INTERMEDIATE 8

Ethyl 2-amino-3-[*N*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionate

Sodium metal (61mg, 2.65mmol) was added to anhydrous ethanol (20ml) and stirred under N_2 for 0.5h. Intermediate 7 (490mg, 0.88mmol) was added and the reaction mixture heated under reflux for 6h. The volatiles were removed *in vacuo* and the residue treated with EtOH (50ml). HCl gas was bubbled through for a short time and the reaction mixture allowed to stand at room temperature for 18h. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (70ml) and saturated aqueous $NaHCO_3$ (30ml). The phases were separated and the aqueous layer re-extracted with ethyl acetate (2 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was chromatographed (silica; 5% MeOH/DCM) affording the title compound as a white foam (240mg, 71%). δH ($CDCl_3$) 9.75 (1H, s), 8.33 (1H, d, J 5.4Hz), 7.62-7.60 (2H, m's), 7.35-7.30 (3H, m's), 4.17 (2H; q, J 7.2Hz), 3.60 (1H, dd, J 7.6, 6.4Hz), 2.93 (1H, dd, J 13.8, 6.4Hz), 2.72 (1H, dd, J 13.8, 7.6Hz), 1.55 (2H, br s) and 1.26 (3H, t, J 7.2Hz); m/z (ESI, 60V) 382 (MH^+).

EXAMPLE 1

Ethyl *N*-(*N'*-acetyl-*D*-thioproline)-2-amino-3-(5-benzenesulphonyloxy-pyrid-2-yl)propionate

HOBT (570mg, 4.22mmol), *N*-acetyl-*D*-thioproline (682mg, 3.90mmol) and EDC (750mg, 3.90mmol) were added sequentially to a stirred solution of Intermediate 2 (1.24g, 3.54mmol) in dry DMF (20ml) and stirred at room temperature for 2h. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (75ml) and 10% aqueous Na_2CO_3 (40ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 50ml). The combined organic extracts were washed with brine (10ml),

dried (Na_2SO_4) and evaporated *in vacuo*. The obtained oil was chromatographed (silica, 3 - 5% methanol/DCM) to afford the title compound as a near colourless glass (1.46g, 81%). δH ($CDCl_3$; approx: 1:1 mixture of diastereoisomers and rotameric species): 8.4-8.35, 8.1-8.02, 7.81-7.76, 7.71-7.45, 7.42-7.25 and 7.15-7.08 (9H, m's, CONH, pyr-H and Aryl-H), 5.10-4.31 (4H, ms, α-CHx2 and NCH_2S), 4.15-4.01 (2H, m, CH_2CH_3), 3.41-3.02 (4H, m, CH_2-pyr and CH_2S), 2.13, 2.10, 2.08 and 1.95 (3H, singlets, NCOMe) and 1.12 (3H, m, CH_2CH_3); m/z (ESI) 508 (MH^+).

EXAMPLE 2

***N*-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-(5-hydroxypyrid-2-yl)propanoic acid**

The compound of Example 1 (1.2g, 2.4mmol) was treated with a solution of $LiOH.H_2O$ (220mg, 5.2mmol) in dioxan (10ml), water (10ml) and methanol (5ml), and stirred at room temperature for 3.5h. The reaction mixture was acidified with acetic acid and the volatiles removed *in vacuo*. The residue was chromatographed [silica; DCM (120 - 100), methanol (20), acetic acid (3), H_2O (2)] affording the title compound (580mg, 72%, slightly contaminated with benzenesulphonic acid). δH (d^6 - DMSO; spectrum shows an approximate 1:1 mixture of diastereoisomers and rotameric species): 8.29, 8.09, 7.98 and 7.83 (1H, doublets, CONH), 7.98 (1H, br s, pyr-H (6)), 7.02 (2H, br s, pyr-H (3 and 4)), 4.88-4.67 (2H, br m, CHαthiopro and NCH_AH_BS), 4.49-4.18 (2H, ms, CHα-CH_2pyr and NCH_AH_BS), 3.37-2.82 (2H, br m, CCH_2S and CH_2-pyr) and 2.05, 1.88, 1.87 and 1.85 (3H, singlets, NCOMe); m/z (ESI) 340 (MH^+).

EXAMPLE 3

***N*-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-[5-(2,6-dichlorobenzyloxy)-pyrid-2-yl]propanoic acid**

A mixture of the compound of Example 2 (450mg, 1.33mmol), 2,6-dichlorobenzyl bromide (669mg, 2.78mmol) and ceasium carbonate (1.34g, 4.11mmol) in dry DMF (10ml) was stirred at room temperature for 6h. The volatiles were removed *in vacuo* and the residue partitoned between EtOAc (70ml) and water (50ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 50ml). The combined

organic extracts were washed with brine (20ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained oil was chromatographed (silica; EtOAc) to afford the di-*O*-alkylated intermediate as a mixture of two diastereoisomers and as a colourless viscous oil (227mg, 26%). This material was treated with a solution of $LiOH.H_2O$ (17mg, 0.41mmol) in dioxan (4ml), water (3ml) and methanol (2ml) at room temperature for 1h. After adding a few drops of acetic acid, the volatiles were removed *in vacuo*. The residue was chromatographed [silica, DCM (200), methanol (20), acetic acid (3), H_2O (2)] to afford the product as a colourless oil. Freeze-drying from aqueous methanol afforded the title compound as a white amorphous solid (130mg, 76%). δH (d^6-DMSO, 390K) (approximately 1:1 mixture of diastereoisomers) 8.27 (1H, d, J 2.5Hz, pyr-H (6)), 7.88 (1H, br d, J ~8Hz, CONH), 7.52-7.39 (4H, ms, pyr-H and Ar-H), 7.21 (1H, dd, J 8.5, 2.5Hz, pyr-H (4)), 5.34 (2H, s, CH_2O), 4.81 (1H, dd, J 7.4, 3.8Hz, CHα-thiopro), 4.77 and 4.74 (1H, overlapping doublets, J 9.3Hz, SH_AH_BN), 4.69 (1H, br m, CHα-CH_2pyr), 4.37 and 4.34 (1H, overlapping doublets, J 9.3Hz, SH_AH_BN), 3.30-3.07 (3H, ms, CH_2pyr and CH_AH_BS), 3.04 (1H, dd, J 11.5, 3.8Hz, CH_AH_BS) and 1.99 and 1.98 (3H, singlets, NCOMe); m/z (ESI) 498 and 500 (MH^+). Found: C, 49.86; H, 4.20; N, 8.33. $C_{21}H_{21}Cl_2N_3O_5S.0.4\ H_2O$ requires C, 49.89; H, 4.35; N, 8.31%.

EXAMPLE 4

***N*-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propanoic acid**

The compound of Example 1 (400mg, 0.79mmol) was treated with a solution of $LiOH.H_2O$ (36mg, 0.86mmol) in dioxan (4ml), H_2O (3ml) and ethanol (2ml) for 1.5h at room temperature. A few drops of acetic acid were added and the volatiles removed *in vacuo*. The residue was chromatographed [silica; DCM (200), methane (20), acetic acid (3), H_2O (2)) to afford the product as a colourless oil. This was freeze-dried from aqueous methanol to afford the title compound as a white amorphous solid (240mg, 64%). δH (d^6-DMSO, 390K; approximately 1:1 mixture of diasteroisomers) 8.17 (1H, singlet with fine couplings, pyr-H (6)), 7.90-7.79 (4H, ms, Ar-H and NHCO), 7.68 (2H, apparent J ~8Hz, Ar-H), 7.43 (1H, dd, J 8.6, 2.8Hz, pyr-H (4)), 7.30 (1H, dd, J 8.6, 3.2Hz, pyr-H (3)), 4.79

(1H, overlapping m, CHαCHpyr), 4.75 (1H, apparent J ~9Hz, NCH_AH_BS), 4.68 (1H, overlapping m, CHαthiopro), 4.38 (1H, apparent J ~9Hz, NCH_AH_BS), 3.33-2.98 (4H, ms, CH_2pyr and CCH_2S) and 1.99 and 1.98 (3H, singlets, NCOMe); m/z (ESI) 480 (MH^+); Found: C, 48.33; H, 4.30; N, 8.34. $C_{20}H_{21}N_3O_7S_2.H_2O$ requires C, 48.28; H, 4.66; N, 8.45%.

EXAMPLE 5

Ethyl 2-[*N*-(2-chloropyrid-3-oyl)-amino]-3-[*N'*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionate

2-Chloronicotinoyl chloride (110mg, 0.63mmol) was added to a stirred solution of Intermediate 8 (240mg, 0.63mmol) and pyridine (50mg, 50µl, 0.63mmol) in dry DCM (5ml), and the reaction stirred under nitrogen fof 2h. The reaction mixture was partitioned between DCM (100ml) and saturated aqueous $NaHCO_3$ (10ml). The phases were separated and the organic layer washed with brine (5ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained white foam was chromatographed (silica, 2% MeOH/DCM) affording the title compound as a white amorphous solid (145mg, 44%) δH ($CDCl_3$) 9.79 (1H, s), 8.35 (1H, dd, J 4.8, 2.0Hz), 8.23 (1H, d, J 8.5Hz), 7.96 (1H, d, J 8.0Hz), 7.91 (1H, dd, J 7.6, 2.0Hz), 7.37 (1H,dd, J 8.5, 2.3Hz), 7.34-7.21 (5H, m), 5.05 (1H, symmetrical m), 4.02 (2H, q, J 7.1Hz), 3.11-2.95 (2H, m) and 1.24 (3H, t, J 7.1Hz); m/z (ESI, 60V), 521 (MH^+).

EXAMPLE 6

2-[*N*-(2-Chloropyrid-3-oyl)-amino]-3-[*N'*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionic acid

The compound of Examaple 5 (135mg, 0.26mmol) was treated with a solution of $LiOH.H_2O$ (23mg, 0.55mmol) in dioxane (2ml), methanol (1ml) and water (2ml) at room temperature for 2h. A few drops of acetic acid were added and the volatiles removed *in vacuo*. The residue was treated with water and the obtained white solid collected by filtration, water-washed and sucked dry, affording the title compound as a white powder (101mg, 80%). δH (d^6-DMSO) 11.16 (1H, s), 8.98 (1H, d, J 8.2Hz), 8.45 (1H, dd, J 4.8, 1.9Hz), 8.26 (1H, d, J 1.9Hz), 8.14 (1H, d, J 8.5Hz), 7.79 (1H,dd, J 8.5,2.2Hz), 7.71 (1H, dd, J 7.5, 1.9Hz), 7.57-7.42 (4H, m's),4.71-4.63 (1H, symmetrical m), 3.20 (1H, dd, J 14.1, 4.8Hz) and 2.98 (1H, dd, J 14.1, 9.8Hz); m/z (ESI, 60V) 493 (MH^+).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with $F(ab)_2$ fragment goat anti-human IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 µl at 2 µg/ml in 0.1M $NaHCO_3$, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 µl containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100µl methanol for 10 minutes followed by another wash. 100µl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100µl 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β-lympho blastoid cell-line JY was used in place of Jurkat cells. The IC_{50} value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5μg/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100μl PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200μl containing 2.5x 10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$-dependent human polymorphonuclear neutrophils adhesion to plastic

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200μl in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100μl 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H_2O_2 (Sigma) and 50μg/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

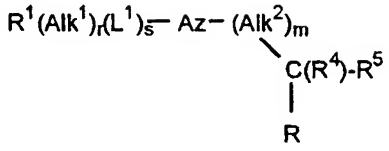
αIIb/β_3 -dependent human platelet aggregation

Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10^8/ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $MgCl_2.H_2O$ 0.427; $CaCl_2$ 0.2; KCl 0.2; D-glucose 1.0; $NaHCO_3$ 1.0; $NaHPO_4.2H_2O$ 0.065). Aggregation was monitored following addition of 2.5μM ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the compounds of the invention generally have IC_{50} values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of 1 μM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of 50μM and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

CLAIMS

1. A compound of formula (1):



(1)

wherein
Az is an optionally substituted monocyclic six-membered nitrogen-containing aromatic group;
R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;
Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;
L^1 is a linker atom or group;
r and s is each zero or an integer 1;
Alk^2 is a straight or branched alkylene chain;
m is zero or an integer 1;
R^4 is a hydrogen atom or a methyl group;
R^5 is a group $-L^2(CH_2)_tR^6$ in which L^2 is a $-N(R^7)CO-$ [where R^7 is a hydrogen atom or a straight or branched alkyl group] or $-N(R^7)CS-$ group, t is zero or the integer 1, and R^6 is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;
R is a carboxylic acid ($-CO_2H$) or a derivative thereof;
and the salts, solvates and hydrates thereof.

2. A compound according to Claim 1 wherein R is a $-CO_2H$ group.

3. A compound according to Claim 1 or Claim 2 wherein Alk^2 is a $-CH_2-$ chain, m is an integer 1 and R^4 is a hydrogen atom.

4. A compound according to any one of Claim 1 to Claim 3 wherein $-(Alk^1)_r(L^1)_s-$ is a $-CH_2O-$, $-S(O)_2O-$ or $-CON(R^8)-$ group where R^8 is a hydrogen atom or an optionally substituted straight or branched alkyl group.

5. A compound according to Claim 4 wherein $-(Alk^1)_r(L^1)_s-$ is a -CONH- group.

6. A compound according to any one of Claim 1 to Claim 5 wherein R^1 is an optionally substituted aromatic or heteroaromatic group

7. A compound according to Claim 6 wherein R^1 is an optionally substituted phenyl, pyridyl or pyrimidinyl group.

8. A compound according to any one of Claim 1 to Claim 7 wherein Az is an optionally substituted pyridyl group.

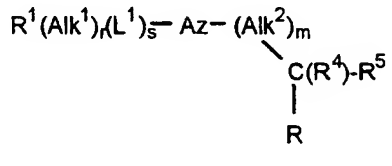
9. A compound according to any one of Claim 1 to Claim 8 wherein R^5 is a $-NHCOR^6$ or $-NHCSR^6$ group.

10. A compound according to any one of the preceding Claims wherein R^6 is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group.

11. A compound according to Claim 10 wherein R^6 is an optionally substituted pyrrolidinyl, thiazolidinyl, phenyl or pyridyl group.

12. A compound which is
N-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-[5-(2,6-dichlorobenzyloxy)-pyrid-2-y]propanoic acid;
N-(*N'*-Acetyl-*D*-thioproline)-2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propanoic acid;
2-[*N*-(2-Chloropyrid-3-oyl)-amino]-3-[*N'*-(dichlorobenzoyl)-6-amino-pyrid-3-yl]propionic acid.
and the salts, solvates and hydrates thereof.

13. A pharmaceutical composition comprising a compound of formula (1):



(1)

wherein
Az is an optionally substituted monocyclic six-membered nitrogen-containing aromatic group;
R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;
Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;
L^1 is a linker atom or group;
r and s is each zero or an integer 1;
Alk^2 is a straight or branched alkylene chain;
m is zero or an integer 1;
R^4 is a hydrogen atom or a methyl group;
R^5 is a group $-L^2(CH_2)_tR^6$ in which L^2 is a $-N(R^7)CO-$ [where R^7 is a hydrogen atom or a straight or branched alkyl group] or $-N(R^7)CS-$ group, t is zero or the integer 1, and R^6 is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;
R is a carboxylic acid ($-CO_2H$) or a derivative thereof;
and the salts, solvates and hydrates thereof;
together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

Inter. ..ional Application No
PCT/GB 99/01741

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12 C07D207/16 C07D213/82 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 10312 A (HOFFMANN LA ROCHE) 4 March 1999 (1999-03-04) claims 1,35,38-42 ---	1,13
X,P	WO 98 58902 A (TANABE SEIYAKU CO ;YAMAGISHI MASAFUMI (JP); TEEGARDEN BRADLEY (US)) 30 December 1998 (1998-12-30) claims; example 254 ---	1-7,9, 10,13
X,P	WO 98 53814 A (HAGMANN WILLIAM K ;MUMFORD RICHARD A (US); KEVIN NANCY J (US); MAC) 3 December 1998 (1998-12-03) claims 15,18-20 ---	1,13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 1999	13/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter..ional Application No
PCT/GB 99/01741

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 98 42662 A (NOVARTIS ERFINDUNGEN VERWALTUN ;NOVARTIS AG (CH)) 1 October 1998 (1998-10-01) claims 1,9; examples 16,70 ---	1,2,8-11
A	US 5 260 277 A (MCKENZIE THOMAS C) 9 November 1993 (1993-11-09) the whole document ---	1,13
X	EP 0 144 230 A (PFIZER LTD ;PFIZER (PA)) 12 June 1985 (1985-06-12) example 5 (7) ---	1-4,6-11
X	B.J. WHITLOCK ET AL.: "Structure and synthesis of lathyrine" JOURNAL OF ORGANIC CHEMISTRY., vol. 30, - 1965 pages 115-118, XP002110766 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 preparation of benzoyl derivative of lathyrine page 116 ---	1
X	O.E. SCHULTZ ET AL : "Analogos of nucleic acid bases as antimetabolites" ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH., vol. 17, no. 8, 1967, pages 1060-1064, XP002110767 EDITIO CANTOR. AULENDORF., DE ISSN: 0004-4172 compound VIII ---	1,4,6,7, 9
X	CHEMICAL ABSTRACTS, vol. 86, no. 25, 20 June 1977 (1977-06-20) Columbus, Ohio, US; abstract no. 190438, HARRIS, ROGER L. N. ET AL: "Potential wool growth inhibitors. 2(1H)-Pyridone analogs of mimosine" XP002110769 abstract -& CHEMICAL ABSTRACTS 10TH COLLECTIVE INDEX., page 8154F XP002110768 AMERICAN CHEMICAL SOCIETY. COLUMBUS., US ISSN: 0097-6474 CAS RN 62812-03-7: alpha-acetylamino-2-ethoxy-4-pyridine-propanoic acid, ethyl ester & AUST. J. CHEM. (1977), 30(3), 649-55 , --- -/--	1-4,6-9

INTERNATIONAL SEARCH REPORT

Inter ..onal Application No
PCT/GB 99/01741

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 54, no. 11, 1960 Columbus, Ohio, US; abstract no. 11021g, YOSHIYA NOIKE: "Synthesis of quinolizine derivatives. " XP002110770 see VIIIa and Benzyl analog of VIII abstract & YAKUGAKU ZASSHI, vol. 79, pages 1514-1518,	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01741

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-11 and 13 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out completely for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds covered by claims 4, 5 and 12. Claim 13 has also been searched in relation to the same pharmaceutical use (see present abstract). The remaining claims have been searched partially.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

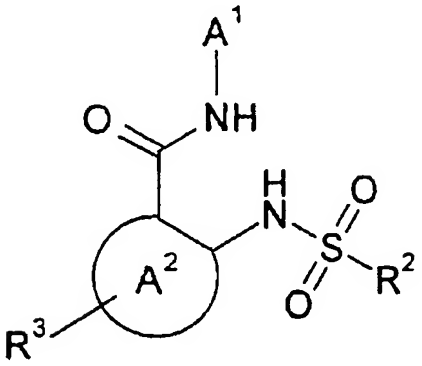
Information on patent family members

Inter..onal Application No
PCT/GB 99/01741

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9910312 A	04-03-1999	AU 9262098 A	16-03-1999
WO 9858902 A	30-12-1998	AU 8163398 A	04-01-1999
WO 9853814 A	03-12-1998	NONE	
WO 9842662 A	01-10-1998	AU 7037298 A	20-10-1998
US 5260277 A	09-11-1993	NONE	
EP 0144230 A	12-06-1985	AT 55393 T	15-08-1990
		CA 1263499 A	28-11-1989
		DK 581684 A	18-06-1985
		GR 81149 A	03-04-1985
		IE 57648 B	10-02-1993
		JP 60155194 A	15-08-1985
		US 4562197 A	31-12-1985

Sulphonylaminocarboxylic acid N-arylamides as guanylate cyclase activators

The present invention relates to compounds of the formula I



I

in which A^1, A^2, R^2 and R^3 have the meanings indicated below, which are valuable pharmaceutical active compounds for the therapy and prophylaxis of diseases, for example of cardiovascular disorders such as high blood pressure, angina pectoris, cardiac insufficiency, thromboses or atherosclerosis. The compounds of the formula I have the ability to modulate the endogenous production of cyclic guanosine monophosphate (cGMP) and are generally suitable for the therapy and prophylaxis of disease states which are associated with a disturbed cGMP balance. The invention relates to the use of compounds of the formula I for the therapy and prophylaxis of the designated disease states and for the production of pharmaceuticals therefore, novel compounds of the formula I, pharmaceutical preparations comprising them and processes for their preparation.

cGMP is an important intracellular messenger, which elicits a number of pharmacological effects by means of the modulation of cGMP-dependent protein kinases, phosphodiesterases and ion channels. Examples are smooth muscle relaxation, the inhibition of platelet activation and the inhibition of smooth muscle cell proliferation and leukocyte adhesion. cGMP is produced by particulate and soluble guanylate cyclases as a response to a number of extracellular and intracellular stimuli. In the case of the particulate guanylate cyclases, the stimulation essentially takes place by means of peptide signal substances, such as the atrial natriuretic

peptide or the cerebral natriuretic peptide. The soluble guanylate cyclases (sGC), which are cytosolic, heterodimeric heme proteins, however, are essentially regulated by a family of low molecular weight, enzymatically formed factors. The most important stimulant is nitrogen monoxide (NO) or a closely relates species. The importance of other factors such as carbon monoxide or the hydroxyl radical is still largely unclarified. The binding of NO to the heme with formation of a pentacoordinated heme-nitrosyl complex is discussed as an activation mechanism of activation by NO. The release associated therewith of the histidine which is bound to the iron in the basal state converts the enzyme into the activated conformation.

Active soluble guanylate cyclases are each composed of one α- and one β-subunit. Several subtypes of the subunits have been described, which differ from one another with respect to sequence, tissue-specific distribution and expression in various stages of development. The subtypes α_1 and β_1 are mainly expressed in the brain and lung, while β_2 is especially found in liver and kidney. The subtype α_2 was detected in human fetal brain. The subunits designated as α_3 and β_3 were isolated from human brain and are homologous to α_1 and β_1. More recent studies point to an α_{2i} subunit, which contains an insert in the catalytic domain. All subunits show great homology in the area of the catalytic domain. The enzymes probably contain one heme per heterodimer, which is bonded via β_1-Cys-78 and/or β_1-His-105 and is part of the regulatory center.

The formation of guanylate cyclase-activating factors can be decreased under pathological conditions or increased degradation thereof can take place as a result of the increased occurrence of free radicals. The decreased activation of the sGC resulting therefrom leads, via the attenuation of the respective cGMP-mediated cell response, for example, to an increase in the blood pressure, to platelet activation or to increased cell proliferation and cell adhesion. As a result, the formation of endothelial dysfunction, atherosclerosis, high blood pressure, stable and unstable angina pectoris, thromboses, myocardial infarct, strokes or erectile dysfunction occurs. The pharmacological stimulation of the sGC offers a possibility for the normalisation of cGMP production and thus allows the treatment or prevention of illnesses of this type.

For the pharmacological stimulation of sGC, until now compounds have almost exclusively been used whose action is based on an intermediate

release of NO, for example organic nitrates. The disadvantage of this method of treatment lies in the development of tolerance and weakening of action and the higher dose which therefore becomes necessary.

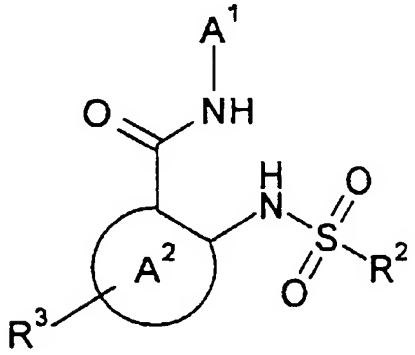
Various sGC stimulators which do not act via a release of NO have been described in a relatively large number of studies by Vesely. The compounds, which are mostly hormones, plant hormones, vitamins or, for example, natural substances such as lizard toxins, however, without exception show only weak effects on cGMP formation in cell lysates (D. L. Vesely, Eur. J. Clin. Invest. 15 (1985) 258; D. L. Vesely, Biochem. Biophys. Res. Comm. 88 (1979) 1244). Stimulation of heme-free guanylate cyclase by protoporphyrin IX was detected by Ignarro et al. (Adv. Pharmacol. 26 (1994) 35). Pettibone et al. (Eur. J. Pharmacol. 116 (1985) 307) describe a hypotensive action for diphenyliodonium hexafluorophosphate and attributed this to a stimulation of sGC. Isoliquiritiginin, which shows a relaxant action on isolated rat aortas, likewise activates sGC according to Yu et al. (Brit. J. Pharmacol. 114 (1995) 1587). Ko et al. (Blood 84 (1994) 4226), Yu et al. (Biochem. J. 306 (1995) 787) and Wu et al. (Brit. J. Pharmacol. 116 (1995) 1973) detected an sGC stimulating activity of 1-benzyl-3-(5-hydroxymethyl-2-furyl)indazole and demonstrated an antiproliferative and platelet-inhibiting action.

A number of sulphonylaminocarboxylic acid N-arylamides of the formula I are already known. Compounds of this type are used, for example, in the production of photographic materials (see, for example, Chemical Abstracts 119, 105 755; 116, 245 151 and 104, 177 628) and, for this purpose, then in general contain in the N-aryl group as substituents easily oxidizable groups such as, for example, two hydroxyl groups in the para-position to one another. For various compounds of the formula I, a pharmacological action has also already been described. Thus, for example, in DE-A-35 23 705, an anthelmintic action is described for a series of 2-phenylsulphonylaminobenzamides. Antiparasitic, antimicrobial or fungicidal actions of 2-sulphonylaminobenzoic acid N-(hetero)arylamides are also mentioned, for example, in EP-A-420 805 and in Chemical Abstracts 122, 136 749; 120, 560; 119, 116 978; 116, 228 237; 116, 207 806; 115, 158 666 and 106, 152 850. According to EP-A-347 168, certain compounds of the formula I having a phenyl pivalate structure are elastase inhibitors and can be used in the treatment of atherosclerosis or arthritis. In Chemical Abstracts 104, 33 896, a psychotropic action is described for

certain 2-sulphonylaminobenzoic acid N-phenoxyphenylamides. Various 2-trifluoromethylsulphonylamino- and 2-methylsulphonylamino-substituted benzamides are described as angiotensin II receptor antagonists having antihypertensive activity in Hypertension 15 (1998) 823, J. Med. Chem. 33 (1990) 1312, EP-A-253 310, EP-A-324 377, EP-A-449 699, EP-A-530 702 and US-A-4 880 804.

Surprisingly, it has now been found that the compounds of the formula I bring about strong guanylate cyclase activation, on account of which they are suitable for the therapy and prophylaxis of illnesses which are associated with a low cGMP level.

The present invention thus relates to the use of compounds of the formula I,



I

in which

A^1 is a radical from the group consisting of phenyl, naphthyl and heteroaryl, which can all be substituted by one or more identical or different radicals R^1;

the ring A^2, which includes the carbon atoms which carry the groups CO-NH- and NH-SO_2R^2, is a benzene ring, a naphthalene ring, a saturated or partially unsaturated 3-membered to 7-membered carbocycle, a saturated, partially unsaturated or aromatic monocyclic 5-membered to 7-membered heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S, or a saturated, partially unsaturated or aromatic bicyclic 8-membered to 10-membered heterocycle, which contains one or more ring heteroatoms from the group consisting of N, O and S;

R^1 is halogen, aryl, CF_3, NO_2, OH, -O-(C_1-C_7)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, -O-aryl, (C_1-C_2)-alkylenedioxy, NR^5R^6, CN, CO-NR^5R^6, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_{10})-alkyl, CO-aryl or (C_1-C_{10})-alkyl, which can be substituted by one or more identical or different radicals R^4;

R^2 is aryl, heterocyclyl, NR^5R^6 or (C_1-C_{10})-alkyl, which can be substituted by one or more identical or different radicals R^4;

R^3 is one or more identical or different substituents from the group consisting of hydrogen, halogen, CF_3, OH, -O-(C_1-C_{10})-alkyl, -O-(C_1-C_7)-alkyl-R^7, -O-aryl, SH, -S-(C_1-C_{10})-alkyl, -S-(C_1-C_7)-alkyl-R^7, -S-aryl, (C_1-C_3)-alkylenedioxy, CN, NO_2, NR^8R^9, CO-NR^5R^6, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, $S(O)_n$-(C_1-C_7)-alkyl, $S(O)_n$-aryl, $S(O)_n$-NR^5R^6 and (C_1-C_7)-alkyl, which can be substituted by one or more identical or different radicals R^4;

R^4 is fluorine, OH, -O-(C_1-C_{10})-alkyl, -O-(C_1-C_7)-alkyl-R^7, -O-aryl, SH, -S-(C_1-C_{10})-alkyl, -S-(C_1-C_7)-alkyl-R^7, -S-aryl, -P(O)(O-(C_1-C_5)-alkyl)$_2$, -P(O)-$(OH)_2$, CN, NR^8R^9, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl or oxo;

R^5 is hydrogen, (C_1-C_{10})-alkyl which can be substituted by one or more identical or different substituents R^4 and/or by aryl, or is aryl, heterocyclyl, CO- (C_1-C_{10})-alkyl, CO-aryl, CO-heterocyclyl, SO_2-(C_1-C_{10})-alkyl, SO_2-aryl or SO_2-heterocyclyl;

R^6, independently of R^5, has one of the meanings indicated for R^5, or R^5 and R^6, together with the nitrogen atom to which they are bonded, form a 5-membered to 8-membered saturated or partially unsaturated ring which, in addition to the nitrogen atom carrying the groups R^5 and R^6, can also contain one or more further ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, (C_1-C_3)-hydroxyalkyl, -(C_1-C_3)-alkyl-O-(C_1-C_4)-alkyl, aryl, CF_3, OH, -O-(C_1-C_7)-alkyl, -O-aryl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, (C_2-C_3)-alkylenedioxy, NR^8R^9, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-

alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, CHO, CO-(C_1-C_5)-alkyl, S(O)$_n$-(C_1-C_4)-alkyl, S(O)$_n$-NH_2, S(O)$_n$-NH-(C_1-C_3)-alkyl, S(O)$_n$-N((C_1-C_3)-alkyl)$_2$, oxo, -$(CH_2)_m$-NH_2, -$(CH_2)_m$-NH-(C_1-C_4)-alkyl and –$(CH_2)_m$-N((C_1-C_4)-alkyl)$_2$, where in the substituent -$(CH_2)_m$-N((C_1-C_4)-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then, together with the nitrogen atom carrying them, form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms, can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^7 is OH, -O-(C_1-C_7)-alkyl, NH_2, -NH-(C_1-C_4)-alkyl or -N((C_1-C_4)-alkyl)$_2$, where in the substituent N((C_1-C_4)-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then, together with the nitrogen atom carrying them, form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^8 is hydrogen or (C_1-C_7)-alkyl, which can be substituted by one or more identical or different substituents from the group consisting of OH, -O-(C_1-C_5)-alkyl, NH_2, -NH-(C_1-C_4)-alkyl and –N((C_1-C_4)-alkyl)$_2$;

R^9, independently of R^8, has one of the meanings of R^8 or is CO-(C_1-C_4)-alkyl;

aryl is phenyl, naphthyl or heteroaryl, which can all be substituted by one or more identical or different substituents from the group consisting of halogen, (C_1-C_5)-alkyl, phenyl, tolyl, CF_3, NO_2, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_3)-alkyl, -N((C_1-C_3)-alkyl)$_2$, NH-CHO, -NH-CO-(C_1-C_5)-alkyl, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_5)-alkyl, S(O)$_n$-(C_1-C_4)-alkyl, S(O)$_n$-phenyl, S(O)$_n$-tolyl, S(O)$_2$-NH_2, S(O)$_2$-NH-(C_1-C_3)-alkyl and S(O)$_2$-N((C_1-C_3)-alkyl)$_2$;

heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle, each of which contain one or more ring heteroatoms from the group consisting of N, O and S;

heterocyclyl is the radical of a monocyclic or polycyclic, 5-membered to 11-membered saturated or partially unsaturated heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, NH_2, -NH-(C_1-C_3)-alkyl, -N$((C_1-C_3)$-alkyl$)_2$, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N$((C_1-C_3)$-alkyl$)_2$, COOH and CO-O-(C_1-C_5)-alkyl;

n is 0, 1 or 2;

m is 2, 3 or 4;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts for the production of a medicament for the activation of soluble guanylate cyclase.

If groups or substituents can occur a number of times in the compounds of the formula I, they can all independently of one another have the indicated meanings and can each be identical or different.

Alkyl radicals can be straight-chain or branched. This also applies if they are contained in other groups, for example in alkoxy groups, alkoxycarbonyl groups or in amino groups, or if they are substituted. Examples of alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, the n-isomers of these radicals, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl. The term alkyl here is expressly also understood as meaning unsaturated alkyl radicals, i.e. alkyl radicals which contain one or more double bonds and/or one or more triple bonds, i.e. alkenyl radicals and alkynyl radicals. Examples of such radicals are the vinyl radical, the 2-propenyl radical (allyl radical), the 2-butenyl radical, the 2-methyl-2-propenyl radical, the ethynyl radical, the 2-propynyl radical (propargyl radical) or the 3-butynyl radical. Furthermore, the term alkyl here is expressly also understood as meaning radicals in which a cyclic system is formed by means of an internal ring closure, the term alkyl thus also includes saturated and partially unsaturated cycloalkyl radicals and cycloalkylalkyl radicals (alkyl substituted by cycloalkyl). Examples of such cycloalkyl radicals are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl,

which all can also be substituted, for example, by one or more identical or different (C_1-C_4)-alkyl radicals, in particular by methyl. Examples of such substituted cycloalkyl radicals are 4-methylcyclohexyl, 4-tert-butylcyclohexyl or 2,3-dimethylcyclopentyl. Furthermore, the term alkyl, if not stated otherwise, here expressly also includes both unsubstituted alkyl radicals and alkyl radicals which are substituted by one or more, for example one, two, three or four, identical or different aryl radicals. The term alkyl here is thus expressly also understood as meaning arylalkyl radicals, for example benzyl radicals, phenylethyl radicals or indanyl radicals.

A saturated or partially unsaturated 3-membered to 7-membered carbocycle representing the ring A^2 can be derived from the monocyclic parent structures cyclopropane, cyclobutane, cyclopentane, cyclohexane or cycloheptane. If the carbocycle is unsaturated, it can contain, for example, a double bond or, in the case of the 5-membered ring, 6-membered ring or 7-membered ring, also two double bonds, which can be isolated or conjugated. Double bonds can be situated in any desired positions with respect to the groups CO-NH- and NH-SO_2-R^2, thus, for example, a double bond can also be situated between the two ring carbon atoms which carry these two groups.

Phenyl radicals, naphthyl radicals and heterocyclic radicals, for example heteroaryl radicals, if not stated otherwise, can be unsubstituted or can carry one or more, for example one, two, three or four, identical or different substituents, which can be situated in any desired positions. If not stated otherwise, the substituents indicated in the definition of the group aryl, for example, can occur in these radicals as substituents. If, in compounds of the formula I, nitro groups are present as substituents, altogether only up to two nitro groups can be present in the molecule. If, for example, phenyl radicals, phenoxy radicals, benzyl radicals or benzyloxy radicals are present in aryl radicals such as, for example, phenyl radicals and/or in heterocyclic radicals as substituents, the benzene ring in these can also in turn be unsubstituted or can be substituted by one or more, for example one, two, three or four, identical or different radicals, for example by radicals from the group consisting of (C_1-C_4)-alkyl, halogen, hydroxyl, (C_1-C_4)-alkoxy, trifluoromethyl, cyano, hydroxycarbonyl, ((C_1-C_4)-alkoxy)carbonyl, aminocarbonyl, nitro, amino, (C_1-C_4)-alkylamino, di-((C_1-C_4)-alkyl)amino and ((C_1-C_4)-alkyl)carbonylamino.

In monosubstituted phenyl radicals, the substituent can be situated in the 2-position, the 3-position or the 4-position, in disubstituted phenyl radicals the substituents can be situated in the 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl radicals, the substituents can be situated in the 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. Tolyl (= methylphenyl) is 2-tolyl, 3-tolyl or 4-tolyl. Naphthyl can be 1-naphthyl or 2-naphthyl. In monosubstituted 1-naphthyl radicals, the substituent can be situated in the 2-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position, in monosubstituted 2-naphthyl radicals in the 1-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position. In higher substituted naphthyl radicals, for example 1-naphthyl radicals or 2-naphthyl radicals which carry two or three substituents, the substituents can also be situated in all possible positions.

Heteroaryl radicals, heterocyclyl radicals, heterocycles representing the ring A^2 and rings which are formed from two groups bonded to a nitrogen atom together with this nitrogen atom, are preferably derived from heterocycles which contain one, two, three or four identical or different ring heteroatoms, particularly preferably from heterocycles which contain one or two or three, in particular one or two, identical or different heteroatoms. If not stated otherwise, the heterocycles can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. They are preferably monocyclic or bicyclic. The rings are preferably 5-membered rings, 6-membered rings or 7-membered rings. Examples of monocyclic and bicyclic heterocyclic systems from which radicals occurring in the compounds of the formula I can be derived are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-dioxole, 1,3-oxazole, 1,2-oxazole, 1,3-thiazole, 1,2-thiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxin, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine, 1,3-thiazepine, indole, benzothiophene, benzofuran, benzothiazole, benzimidazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, thienothiophenes, 1,8-naphthyridine and other naphthyridines, pteridine, or phenothiazine, all in each case in saturated form (perhydro form) or in partially unsaturated form (for example dihydroform and tetrahydro form) or in maximally unsaturated form if the

forms concerned are known and stable. The suitable heterocycles thus also include, for example, the saturated heterocycles pyrrolidine, piperidine, piperazine, morpholine and thiomorpholine. The degree of saturation of heterocyclic groups is indicated in the individual definitions. Unsaturated heterocycles can contain, for example, one, two or three double bonds in the ring system. 5-Membered rings and 6-membered rings in monocyclic and polycyclic heterocycles can in particular also be aromatic.

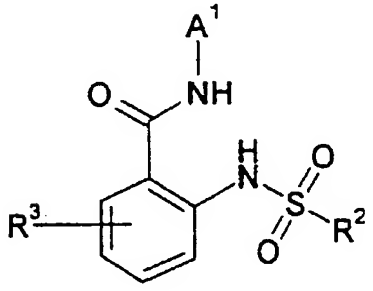
The radicals derived from these heterocycles can be bonded via any suitable carbon atom. Nitrogen heterocycles which carry a hydrogen atom (or a substituent) on a ring nitrogen atom, for pyrrole, imidazole, pyrrolidine, morpholine, piperazine etc. can also be bonded via a ring nitrogen atom, in particular if the nitrogen heterocycle concerned is bonded to a carbon atom. A thienyl radical can be present, for example, as a 2-thienyl radical or 3-thienyl radical, a furan radical as a 2-furyl radical or 3-furyl radical, a pyridyl radical as a 2-pyridyl radical, 3-pyridyl radical or 4-pyridyl radical, a piperidine radical as a 1-piperidyl radical, 2-piperidyl radical, 3-piperidyl radical or 4-piperidyl radical, a thiomorpholine radical as a 2-thiomorpholinyl radical, 3-thiomorpholinyl radical or 4-thiomorpholinyl radical (= thiomorpholino radical). A radical bonded via a carbon atom, which is derived from 1,3-thiazole or from imidazole, can be bonded via the 2-position, the 4-position or the 5-position.

If not stated otherwise, the heterocyclic groups, such as, for example, heteroaryl radicals, can be unsubstituted or can carry one or more, for example one, two, three or four, identical or different substituents. The substituents in heterocycles can be situated in any desired positions, for example in the 3-position and/or in the 4-position and/or in the 5-position in a 2-thienyl radical or 2-furyl radical, in the 2-position and/or in the 4-position and/or in the 5-position in a 3-thienyl radical or 3-furyl radical, in the 3-position and/or in the 4-position and/or in the 5-position and/or in the 6-position in a 2-pyridyl radical, in the 2-position and/or in the 4-position and/or in the 5-position and/or in the 6-position in a 3-pyridyl radical, in the 2-position and/or in the 3-position and/or in the 5-position and/or in the 6-position in a 4-pyridyl radical. If not stated otherwise, the substituents which can occur are, for example, the substituents indicated in the definition of the group aryl, in the case of saturated or partially unsaturated heterocycles as further substituents also the oxo group and the thioxo group. Substituents on a heterocycle and substituents on a carbocycle can

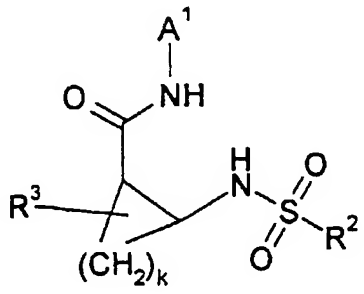
also form a ring, thus further rings can be fused to a ring system so that, for example, cyclopenta-fused, cyclohexa-fused or benzo-fused rings can be present. Suitable substituents on a substituted nitrogen atom of a heterocycle are in particular, for example, unsubstituted (C_1-C_5)-alkyl radicals and aryl-substituted alkyl radicals, aryl radicals, acyl radicals such as CO-(C_1-C_5)-alkyl, or sulphonyl radicals such as SO_2-(C_1-C_5)-alkyl. Suitable nitrogen heterocycles can also be present as N-oxides or as quaternary salts having an anion derived from a physiologically tolerable acid as a counterion. Pyridyl radicals can be present, for example, as pyridine N-oxides.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

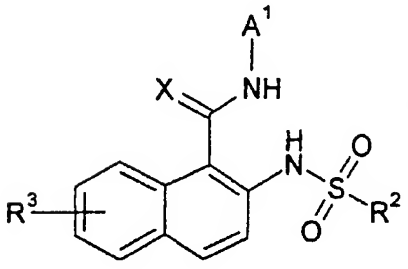
Without restricting the present invention, examples of groups of compounds which can be used according to the invention are shown in the formulae Ia, Ib, Ic, Id, Ie, If, Ig and Ih, in which A^2 in the formula I has specific meanings. In the formulae Ia, Ib, Ic, Id, Ie, If, Ig and Ih, A^1, R^2 and R^3 have the meanings indicated above for the formula I, the number k in the formula Ib is 1, 2, 3, 4 or 5.



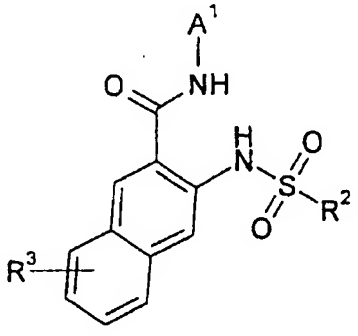
Ia



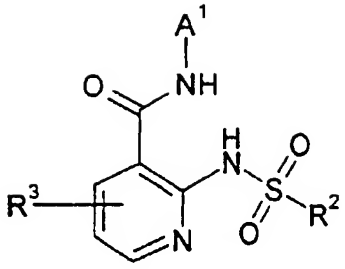
Ib



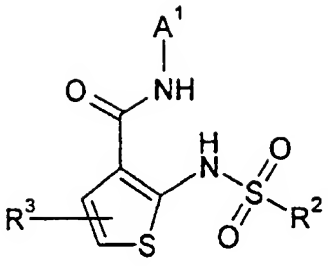
Ic



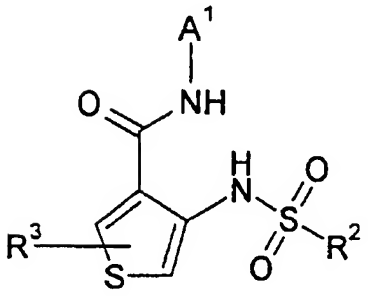
Id



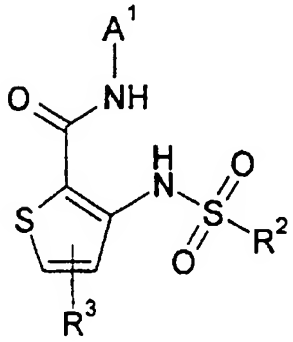
Ie



If



Ig



Ih

The present invention includes all stereoisomeric forms of the compounds of the formula I. Asymmetric centres contained in the compounds of the formula I can all independently of one another have the S configuration or the R configuration. The invention includes all possible enantiomers and diastereomers, as well as mixtures of two or more stereoisomeric forms, for example mixtures of enantiomers and/or diastereomers, in all ratios. Enantiomers are thus included by the invention in enantiomerically pure form, both as dextrorotatory and as levorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the presence of cis/trans isomerism, the invention relates both to the cis form and the trans form and mixtures of these forms in all ratios. Individual stereoisomers can be prepared, if desired, by resolution of a mixture according to customary methods, for example by chromatography or crystallisation, by use of stereochemically homogeneous starting substances in the synthesis or by stereoselective synthesis. If appropriate, derivatisation can be carried out before separation of stereoisomers. The separation of a stereoisomer mixture can be carried out at the stage of the compounds of the formula I or at the stage of an intermediate in the course of the synthesis. If mobile hydrogen atoms are present, the present invention also includes all tautomeric forms of the compounds of the formula I.

If the compounds of the formula I contain one or more acidic or basic groups, the invention also relates to the corresponding physiologically or toxicologically tolerable salts, in particular the pharmaceutically utilizable salts. Thus the compounds of the formula I which contain acidic groups can be present in these groups, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts and can be used according to the invention. Examples of such salts are sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula I which contain one or more basic, i.e. protonatable, groups can be present in the form of their acid addition salts with physiologically tolerable inorganic or organic acids and can be used according to the invention, for example as salts with hydrogen chloride, hydrogen bromide, phosphoric acid, sulphuric acid, nitric acid, methanesulphonic acid, p-toluenesulphonic acid, naphthalenedisulphonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfamic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid etc. If the compounds of the formula I simultaneously contain acidic and basic groups in the molecule, in addition to the salt forms outlined the invention also includes internal salts or betaines (zwitterions). Salts can be obtained from the compounds of the formula I by customary processes known to the person skilled in the art, for example by combination with an organic or inorganic acid or base in a solvent or dispersant, or alternatively from other salts by anion exchange or cation exchange.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols, and also derivatives of the compounds of the formula I such as, for example, esters, and prodrugs and active metabolites.

A^1 is preferably phenyl, naphthyl or bicyclic heteroaryl, which can all be substituted by one or more identical or different radicals R^1. Bicyclic heteroaryl representing A^1 is particularly preferably bicyclic heteroaryl having 10 ring members, which preferably contains one or two nitrogen atoms, in particular a nitrogen atom, as ring heteroatoms. Very particularly

preferably, bicyclic heteroaryl representing A^1 is a radical derived from quinoline.

A^2, together with the two atoms carrying the group R^2-SO_2-NH and the group CO-NH, preferably forms an aromatic ring, particularly preferably a benzene ring or a thiophene ring.

A^1 can be unsubstituted, that is only carry hydrogen atoms, or can be substituted as indicated by one or more, for example one, two, three or four, identical or different radicals R^1. Preferably, a substituted radical A^1 is substituted by one, two or three, in particular one or two, radicals R^1. Radicals R^1 are preferably bonded to carbon atoms in A^1 which are not directly adjacent to the carbon atom which carries the group CO-NH. If A^1 is phenyl, radicals R^1 are particularly preferably in the meta-position and/or in the para-position, relative to the carbon atom which carries the group CO-NH. If a phenyl radical representing A^1 carries a radical R^1, this in many cases is particularly advantageous in the para-position. If a phenyl radical representing A^1 carries a trifluoromethyl group as a radical R^1, this is preferably in the meta-position. If a phenyl radical representing A^1 carries two radicals R^1 representing chlorine, the two chlorine atoms are preferably in positions 3 and 4.

Preferred radicals R^1 are halogen, in particular chlorine, trifluoromethyl, (C_3-C_7)-alkyl, carboxymethyl, $CONR^5R^6$, 5-membered to 7-membered heterocyclyl, -O-aryl, -CO-(C_1-C_{10})-alkyl, -CO-aryl, -NH-CO-(C_1-C_{10})-alkyl, -NH-CO-aryl, -N(CO-(C_1-C_{10})-alkyl)$_2$, -N(CO-aryl)$_2$, -NH-SO_2-(C_1-C_{10})-alkyl, -NH-SO_2-aryl, -N(SO_2-aryl)$_2$ and –N(SO_2-(C_1-C_{10})-alkyl)$_2$, where all alkyl radicals can be substituted by one or more identical or different radicals R^4. In a group $CONR^5R^6$ representing R^1, R^5 and R^6, together with the nitrogen atom to which they are bonded, preferably form a 5-membered to 8-membered saturated or partially unsaturated ring, which in addition to the nitrogen atom carrying the groups R^5 and R^6 can also contain one or more further ring heteroatoms from the group consisting of N, O and S and which can be substituted as indicated above by one or more identical or different substituents. A group of particularly preferred radicals R^1 is formed by the radicals halogen, in particular chlorine, trifluoromethyl, -O-aryl, -NH-CO-(C_1-C_{10})-alkyl, -NH-CO-aryl, -NH-SO_2-(C_1-C_{10})-alkyl and –NH-SO_2-aryl, where all alkyl radicals can be

substituted by one or more identical or different radicals R^4. A further group of particularly preferred radicals R^1 is formed by the radicals $CONR^5R^6$, -CO-(C_1-C_{10})-alkyl, -CO-aryl, -NH-CO-(C_1-C_{10})-alkyl, -NH-CO-aryl, -N(CO-(C_1-C_{10})-alkyl)$_2$, -N(CO-aryl)$_2$, -NH-SO_2-(C_1-C_{10})-alkyl, -NH-SO_2-aryl, -N(SO_2-aryl)$_2$ and –N(SO_2-(C_1-C_{10})-alkyl)$_2$, where all alkyl radicals can be substituted by one or more identical or different radicals R^4.

R^2 is preferably aryl, particularly preferably phenyl or 5-membered or 6-membered heteroaryl, where the radicals can be unsubstituted or substituted as indicated above. Very particularly preferably, R^2 is phenyl, thienyl or pyrazolyl, which can all in each case be substituted by one or two identical or different radicals from the group consisting of halogen, CF_3 and (C_1-C_3)-alkyl.

The rings representing A^2 can be unsubstituted, that is only carry R^3 representing hydrogen, or be substituted as indicated, that is carry one or more radicals R^3 other than hydrogen. The other substituent positions on the ring A^2, which do not carry any radical R^3 other than hydrogen, carry hydrogen atoms. If the ring A^2 carries one or more radicals R^3 which are other than hydrogen, it preferably carries one or two radicals R^3 of this type, in particular a radical R^3 of this type. Radicals R^3 of this type are preferably in those positions of the ring A^2 which are not directly adjacent to the groups CO-NH and R^2SO_2-NH. If A^2 is a saturated or partially unsaturated carbocycle, R^3 of this type is preferably (C_1-C_4)-alkyl, in particular methyl. If A^2 is an aromatic ring, in particular if A^2 is a benzene ring, R^3 of this type is preferably (C_1-C_3)-alkyl, methoxy, halogen or CF_3, particularly preferably methyl or chlorine. If A^2 is an aromatic ring, in particular a benzene ring, it is very particularly preferred if this carries a chlorine atom as a substituent, that is if a radical R^3 representing chlorine is present and the other substituent positions on the benzene ring carry hydrogen atoms. If A^2 is a benzene ring, radicals R^3 other than hydrogen are preferably in positions 4 and/or 5. If only one radical R^3 of this type is present on a benzene ring representing A^2, this radical is preferably in position 5 (relative to the group CO-NH in the 1-position).

If a group is substituted by one or more radicals R^4, it is preferably substituted by one, two or three, in particular one or two, identical or

different radicals R^4. R^4 is preferably hydroxyl, (C_1-C_4)-alkyloxy, di-((C_1-C_4)-alkyl)amino or heteroaryl.

R^5 and R^6 are preferably independently of one another hydrogen, (C_1-C_9)-alkyl, -(C_1-C_3)-alkyl-O-(C_1-C_4)-alkyl or 5-membered or 6-membered aryl or, together with the nitrogen atom carrying R^5 and R^6, form a 5-membered to 7-membered heterocycle, which in addition to the nitrogen atom carrying the groups R^5 and R^6, can also contain a further ring heteroatom from the group consisting of N, O and S and which can be substituted by one or more, for example one, two, three or four, identical or different radicals as indicated above, in particular by radicals from the group consisting of (C_1-C_3)-alkyl, 5-membered aryl and 6-membered aryl. Particularly preferably, R^5 and R^6, together with the nitrogen atom carrying them, form a 5-membered to 7-membered heterocycle which in addition to the nitrogen atom carrying the groups R^5 and R^6 can also contain a further ring heteroatom from the group consisting of N, O and S and which can be substituted by one or more, for example one, two, three or four, identical or different radicals as indicated above, in particular by radicals from the group consisting of (C_1-C_3)-alkyl, 5-membered aryl and 6-membered aryl. Very particularly preferably, such a ring, which is formed from R^5 and R^6 together with the nitrogen atom carrying them, is derived from morpholine, thiomorpholine, 1,1-dioxo-thiomorpholine, 1-oxothiomorpholine, 3,5-dimethylmorpholine, cis-3,5-dimethylmorpholine, 1-(pyrimidin-2-yl)piperazine, piperidin-4-carboxamide, 1-(2-hydroxyethyl)piperazine, 1-methylpiperazine, 1-ethylpiperazine, from 1-arylpiperazines, from ethyl piperazine-1-carboxylate, piperidine, 2-methylpiperidine, 4-hydroxypiperidine, from 4-oxopiperidine or a ketal thereof such as 1,4-dioxa-8-azaspiro[4.5]decane, from tetrahydropyridine, tetrahydropyrimidine, 1-methylhomopiperazine, thiazolidine, pyrroline, 3-hydroxypyrrolidine, 1,2,3,4-tetrahydroisoquinoline or 2,3-dihydro-1H-isoindole, where the ring is bonded via the ring nitrogen atom or, in the case of the piperazine derivatives, via the nonsubstituted ring nitrogen atom. Especially preferred, such a ring, which is formed from R^5 and R^6 together with the nitrogen atom carrying them, is derived from morpholine, thiomorpholine, 1,1-dioxothiomorpholine, 1-oxothiomorpholine, 3,5-dimethylmorpholline, cis-3,5-dimethylmorpholine, 1-(pyrimidin-2-yl)-piperazine, piperidine-4-carboxamide, 1,2,3,4-tetrahydroisoquinoline or 2,3-dihydro-1H-isoindole.

R^8 is preferably hydrogen, $(C_1$-$C_3)$-alkyl, di-$((C_1$-$C_4)$-alkyl)amino or -$(C_1$-$C_3)$-alkyl-O-$(C_1$-$C_4)$-alkyl.

R^9 is preferably hydrogen, $(C_1$-$C_3)$-alkyl or acetyl.

Aryl is preferably phenyl or heteroaryl, in particular phenyl or 5-membered or 6-membered heteroaryl. Preferred substituents in aryl radicals are halogen, CF_3, $(C_1$-$C_3)$-alkyl, cyano, nitro and $(C_1$-$C_3)$-alkyloxy, particularly preferred substituents are CF_3, chlorine, methyl and methoxy.

Heteroaryl preferably represents radicals which are derived from the heteroaromatics thiophene, pyrazole, thiazole, oxazole, pyridine, pyrimidine, pyridazine and tetrazole.

Heterocyclyl preferably represents radicals which are derived from saturated heterocycles, in particular radicals which are derived from pyrrolidine, piperidine, from N-alkylpiperazines, from morpholine, from dialkylmorpholines, from thiomorpholine or tetrahydrofuran.

If a group $S(O)_n$ is bonded to a nitrogen atom, the number n therein is preferably 1 or 2, particularly preferably 2.

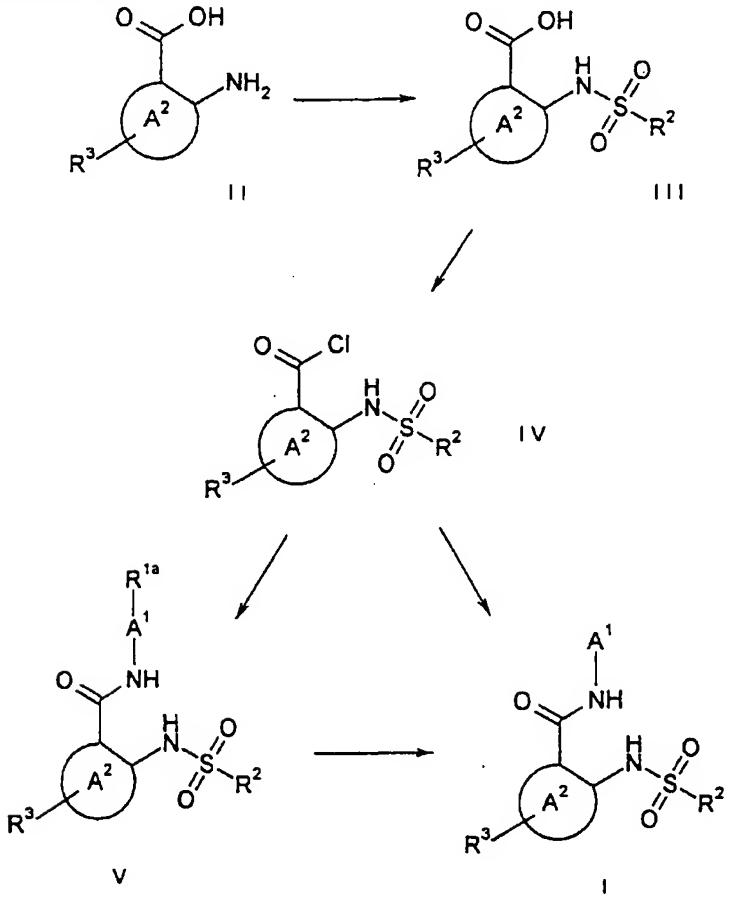
Preferred compounds according to the present invention are compounds of the formula I in which one or more of the radicals contained therein have preferred meanings, where all combinations of preferred substituent definitions are the subject of the present invention. Also, of all preferred compounds of the formula I, the present invention relates to all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts. A group of preferred compounds according to the present invention is formed, for example, from those compounds of the formula I in which A^1 is phenyl which carries a radical R^1 in the 4-position; the ring A^2 which includes the carbon atoms which carry the groups CO-NH- and NH-SO_2R^2 is a benzene ring or a thiophene ring; and R^1 is a substituent from the group consisting of CO-$(C_1$-$C_{10})$-alkyl, CO-aryl, CO-NR^5R^6, -NH-CO-$(C_1$-$C_{10})$-alkyl, -NH-CO-aryl, -N(CO-$(C_1$-$C_{10})$-alkyl$)_2$, -N(CO-aryl$)_2$, -NH-SO_2-$(C_1$-$C_{10})$-alkyl, -NH-SO_2-aryl, -N(SO_2-$(C_1$-$C_{10})$-alkyl$)_2$ and –N(SO_2-aryl$)_2$, in which all alkyl radicals can be substituted by

one or more identical or different radicals R^4; in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts.

Compounds of the formula I can be prepared according to or analogously to the processes described in the literature. Reference is expressly made here to the corresponding contents of documents in which compounds of the formula I are already described, for example DE-A-35 23 705 and its equivalents. The corresponding contents of these documents is part of the present disclosure. The preparation of compounds of the formula I is moreover explained below.

According to scheme 1, an aminocarboxylic acid of the formula II can first be reacted with a sulphonyl chloride of the formula R^2-SO_2-Cl or a sulphonic anhydride in the presence of a base in a solvent such as water, pyridine or an ether.

Scheme 1



Suitable bases are inorganic bases such as, for example, sodium carbonate or organic bases such as, for example, pyridine or triethylamine. The sulphonylaminocarboxylic acid of the formula III obtained can then be activated, for example, by reaction with a chlorinating agent such as, for example, phosphorus pentachloride, phosphorus oxychloride or thionyl chloride in an inert solvent to give an acid chloride of the formula IV and then reacted with an arylamine. The activation of the carboxylic acid group in the compound of the formula III, however, can also be carried out in another way, for example by one of the numerous methods familiar to the person skilled in the art, which are used in peptide chemistry for the linkage of amide bonds, for example by conversion into a mixed anhydride or an activated ester or using a carbodiimide such as dicyclohexylcarbodiimide.

The reaction of the activated sulphonylaminocarboxylic acid with an arylamine is advantageously carried out in an inert solvent such as, for example, pyridine, tetrahydrofuran or toluene with without without[1] addition of an inert auxiliary base, for example of a tertiary amine or of pyridine. If the arylamine employed in the reaction with the activated carboxylic acid already contains the desired substituent(s) R^1 in the group A^1, the arylamine thus has the formula A^1-NH_2, in which the group A^1 as indicated above can contain one or more substituents R^1; thus the reaction leads directly to the final product of the formula I. The activated carboxylic acids, however, can also first be reacted with an arylamine of the formula R^{1a}-A^1-NH_2, in which R^{1a} is hydrogen or one or more of the groups R^1 which can be contained as substituents in A^1, or R^{1a} is one or more groups which can be converted into groups R^1 according to the above definition. For example, R^{1a} can be a hydrogen atom which is replaced in an electrophilic reaction by another radical such as, for example, a halogen atom or an aldehyde group, or an ester group which is converted into an amide group. The conversion of the reaction product of the formula V first obtained into a compound of the formula I can be carried out by standard processes.

Compounds of the formula I can also be obtained, for example, by first activating a suitably substituted nitrocarboxylic acid of the formula VI, for

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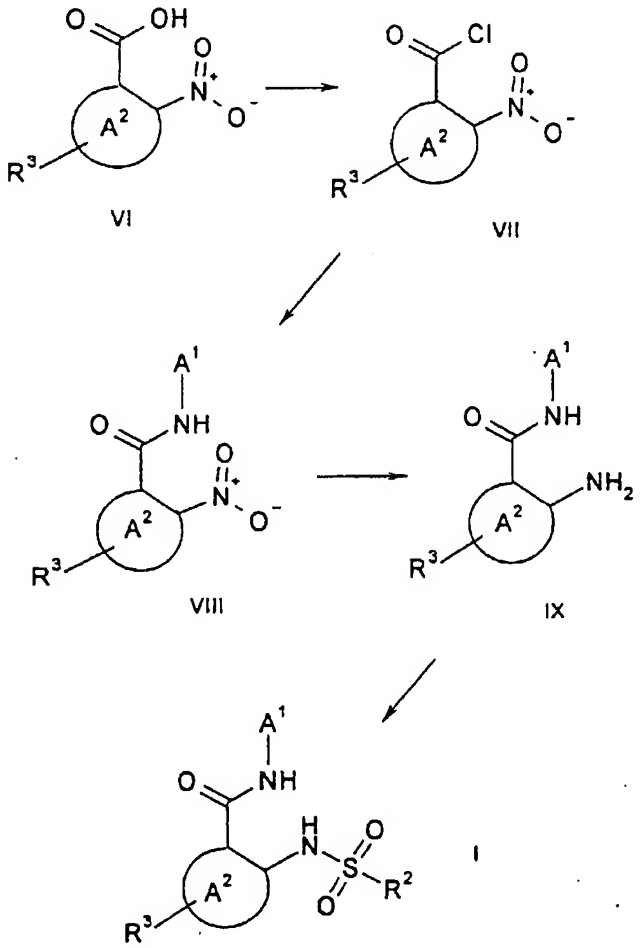
[1] Translator's note: this is a literal translation of the relevant section of the source text, although it doesn't read very well in English.

example by conversion into the corresponding acid chloride of the formula VII or in another way, and then reacted, for example, with a substituted arylamine of the formula A^1-NH_2 analogously to the processes described above (see Scheme 2).

Scheme 2



Before the nitro group is reduced to the amino group in the nitro intermediate products of the formula VIII obtained, the activating action of the nitro group on the ring A^2 can be utilized and a suitable radical R^3, for example a halogen atom, can be replaced by another radical R^3 by reaction with a nucleophile, for example an amine. The reduction of the nitro group to the amino group can be carried out, for example, by catalytic hydrogenation in the presence of a noble metal catalyst or preferably in the presence of Raney nickel in a solvent such as ethanol, glacial acetic acid or

ethanolic hydrochloric acid, or by reduction with a base metal such as tin, zinc or iron in the presence of acid. The reduction can also be carried out, for example, with tin(II) chloride or by reaction with sodium dithionite, advantageously, for example, in a mixture of methanol, tetrahydrofuran and water as the solvent. The sulphonylation of the amino group in the reduction product of the formula IX using an activated sulphonic acid derivative analogously to the reactions described above, for example using a sulphonyl chloride in the presence of pyridine, finally affords the compound of the formula I. Instead of an arylamine of the formula A^1-NH_2, an arylamine of the formula R^{1a}-A^1-NH_2 can also in turn be employed, in which R^{1a} has the meaning indicated above, and the group or the groups R^{1a} are then converted into the group or the groups R^1.

All reactions for the synthesis of the compounds of the formula I are well known per se to the person skilled in the art and can be carried out under standard conditions. Closer details to this end are found, for example, in Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York. Depending on the conditions in the individual case, it can also be advantageous or necessary, in order to avoid side reactions in the synthesis of the compounds of the formula I, to temporarily block certain functional groups by the introduction of protective groups and later to liberate them again or first to employ functional groups in the form of precursors from which the desired functional group is then produced in a later step. Such synthesis strategies and the protective groups or precursors suitable for the individual case are known to the person skilled in the art. The compounds of the formula I obtained can optionally be purified by customary purification methods, for example by recrystallisation or chromatography. Starting compounds for the preparation of the compounds of the formula I are commercially obtainable or can be prepared according to or analogously to literature procedures.

The compounds of the formula I bring about an increase in the cGMP concentration by means of the activation of soluble guanylate cyclase (sGC) and are therefore valuable agents for the therapy and prophylaxis of illnesses which are associated with a low or reduced cGMP level or are caused by such a level or for whose therapy or prophylaxis an increase or normalisation in the cGMP level present is desired. The activation of sGC

by the compounds of the formula I can be investigated, for example, in the activity assay described below.

Illnesses and pathological conditions which are associated with a low cGMP level or in which an increase or normalisation in the cGMP level is desired and for whose therapy and prophylaxis compounds of the formula I can be employed are, for example, cardiovascular disorders such as endothelial dysfunction, diastolic dysfunction, atherosclerosis, high blood pressure, stable and unstable angina pectoris, thromboses, restenoses, myocardial infarct, strokes, cardiac insufficiency or pulmonary hypertension, or, for example, erectile dysfunction, bronchial asthma, chronic renal insufficiency and diabetes. Compounds of the formula I can moreover be employed in the therapy of liver cirrhosis and for improving restricted learning capacity or memory power. Preferably, the compounds of the formula I are employed in cardiovascular disorders such as endothelial dysfunction, diastolic dysfunction, atherosclerosis, high blood pressure, stable and unstable angina pectoris, thromboses, restenoses, myocardial infarct, strokes, cardiac insufficiency or pulmonary hypertension, in erectile dysfunction or for improving restricted learning capacity or memory power.

The compounds of the formula I and their physiologically tolerable salts can thus be used in animals, preferably in mammals, and in particular in man, as pharmaceuticals on their own, in mixtures with one another or together with other active compounds. The present invention therefore in particular also relates to the use of compounds of the formula I and their physiologically tolerable salts for the production of a medicament for the therapy or prophylaxis of the abovementioned syndromes, and the use for the production of a medicament for the increasing or normalisation of a disturbed cGMP balance. The invention likewise relates to the use of the compounds of the formula I and their physiologically tolerable salts for the activation of soluble guanylate cyclase, their use for the therapy or prophylaxis of the abovementioned syndromes and their use for the increasing or normalisation of a disturbed cGMP balance.

Pharmaceuticals according to the present invention can be administered orally, for example in the form of pills, tablets, film-coated tablets, coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the

form of suppositories. Administration, however, can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously in the form of injection solutions or infusion solutions. Further possible administration forms are, for example, percutaneous or topical application, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or administration by inhalation in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The preferred administration form depends, for example, on the illness to be treated and its severity.

The medicaments according to the invention can be produced according to known standard processes for the production of pharmaceutical preparations. For this, one or more compounds of the formula I and/or their physiologically tolerable salts are brought, together with one or more solid or liquid pharmaceutical vehicles and/or additives or auxiliaries and, if desired, in combination with other pharmaceutical active compounds having therapeutic or prophylactic action, into a suitable administration form or dose form, which can then be used as a pharmaceutical in human or veterinary medicine. The pharmaceutical preparations contain a therapeutically or prophylactically active dose of the compounds of the formula I and/or their physiologically tolerable salts, which normally makes up 0.5 to 90% by weight of the pharmaceutical preparation.

For the production, for example, of pills, tablets, coated tablets and hard gelatin capsules, it is possible to use lactose, starch, for example corn starch, or starch derivatives, talc, stearic acid or its salts, etc. Vehicles for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils etc. Suitable vehicles for the preparation of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, physiological saline solution, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol, vegetable oils etc. The compounds of the formula I and their physiologically tolerable salts can also be lyophilised and the lyophilisates obtained used, for example, for the production of injection preparations or infusion preparations. Suitable vehicles for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid.

In addition to the active compounds and vehicles, the pharmaceutical preparations can additionally contain customary additives, for example

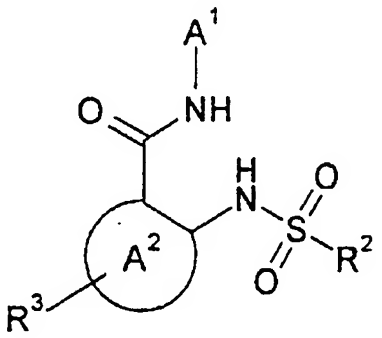
fillers, disintegrants, binders, lubricants, wetting agents, stabilisers, emulsifiers, dispersants, preservatives, sweetening agents, colorants, flavourings or aromatisers, thickening agents, diluents, buffer substances, furthermore solvents or solubilisers or agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

The dose of the active compound of the formula I to be administered and/or of one of physiologically tolerable salts depends on the individual case and is to be suited to the individual conditions as customary for an optimal action. Thus it depends on the nature and severity of the illness to be treated, on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the potency and duration of action of the compounds employed, on whether the therapy is acute or chronic or prophylaxis is carried out, and on whether further active compounds are administered in addition to compounds of the formula I. In general, a daily dose of approximately 0.01 to 100 mg/kg, preferably 0.1 to 10 mg/kg, in particular 0.3 to 5 mg/kg (in each case mg/kg of body weight) is appropriate in the case of administration to an adult of about 75 kg in weight to achieve the desired action. The daily dose can be administered in a single dose or, in particular in the case of administration of relatively large amounts, divided into a number of, for example two, three or four, individual doses. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated. Pharmaceutical preparations normally contain 0.2 to 500 mg, preferably 1 to 200 mg, of active compound of the formula I and/or its physiologically tolerable salts.

The compounds of the formula I activate soluble guanylate cyclase, especially by binding in the heme binding pocket of the enzyme. On account of this property, apart from as pharmaceutical active compounds in human medicine and veterinary medicine, they can also be employed as a scientific tool or as an aid for biochemical investigations in which an effect on guanylate cyclase of this type is intended, and also for diagnostic purposes, for example in the in vitro diagnosis of cell or tissue samples. In addition, the compounds of the formula I and their salts, as already mentioned above, can serve as intermediates for the preparation of further pharmaceutical active compounds.

In addition to already known compounds, the formula I with the above general definition of the radicals also includes compounds which have not

yet been described. The present invention also relates to the not yet known compounds of the formula I as such. The present invention thus also relates to compounds of the formula Ii,



Ii

in which

A^1 is a radical from the group consisting of phenyl, naphthyl and heteroaryl, which can all be substituted by one or more identical or different radicals R^1;

the ring A^2, which includes the carbon atoms which carry the groups CO-NH- and NH-SO_2R^2, is a benzene ring, a naphthalene ring, a saturated or partially unsaturated 3-membered to 7-membered carbocycle, a saturated, partially unsaturated or aromatic monocyclic 5-membered to 7-membered heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S, or a saturated, partially unsaturated or aromatic bicyclic 8-membered to 10-membered heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S;

R^1 is halogen, aryl, CF_3, NO_2, OH, -O-(C_1-C_7)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, -O-aryl, (C_1-C_2)-alkylenedioxy, NR^5R^6, CN, CO-NR^5R^6, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_{10})-alkyl, CO-aryl or (C_1-C_{10})-alkyl which can be substituted by one or more identical or different radicals R^4;

R^2 is aryl, heterocyclyl, NR^5R^6;

R^3 is one or more identical or different substituents from the group consisting of halogen, CF_3, OH, -O-(C_1-C_{10})-alkyl, -O-(C_1-C_7)-alkyl-R^7, -O-aryl, SH, -S-(C_1-C_{10})-alkyl, -S-(C_1-C_7)-alkyl-R^7, -S-aryl, (C_1-C_3)-

alkylenedioxy, CN, NO_2, NR^8R^9, $CO\text{-}NR^5R^6$, COOH, CO-O-$(C_1\text{-}C_5)$-alkyl, heterocyclyl, $S(O)_n$-$(C_1\text{-}C_7)$-alkyl, $S(O)_n$-aryl, $S(O)_n\text{-}NR^5R^6$ and $(C_1\text{-}C_7)$-alkyl, which can be substituted by one or more identical or different radicals R^4;

R^4 is fluorine, OH, -O-$(C_1\text{-}C_{10})$-alkyl, -O-$(C_1\text{-}C_7)$-alkyl-R^7, -O-aryl, SH, -S-$(C_1\text{-}C_{10})$-alkyl, -S-$(C_1\text{-}C_7)$-alkyl-R^7, -S-aryl, -P(O)(O-$(C_1\text{-}C_5)$-alkyl)$_2$, -P(O)-$(OH)_2$, CN, NR^8R^9, $CO\text{-}NH_2$, CO-NH-$(C_1\text{-}C_3)$-alkyl, CO-N($(C_1\text{-}C_3)$-alkyl)$_2$, COOH, CO-O-$(C_1\text{-}C_5)$-alkyl, heterocyclyl or oxo;

R^5 is hydrogen, $(C_1\text{-}C_{10})$-alkyl which can be substituted by one or more identical or different substituents R^4 and/or by aryl, or is aryl, heterocyclyl, CO- $(C_1\text{-}C_{10})$-alkyl, CO-aryl, CO-heterocyclyl, SO_2-$(C_1\text{-}C_{10})$-alkyl, SO_2-aryl or SO_2-heterocyclyl;

R^6, independently of R^5, has one of the meanings indicated for R^5, or R^5 and R^6, together with the nitrogen atom to which they are bonded, form a 5-membered to 8-membered saturated or partially unsaturated ring which, in addition to the nitrogen atom carrying the groups R^5 and R^6, can also contain one or more further ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, $(C_1\text{-}C_5)$-alkyl, $(C_1\text{-}C_3)$-hydroxyalkyl, -$(C_1\text{-}C_3)$-alkyl-O-$(C_1\text{-}C_4)$-alkyl, aryl, CF_3, OH, -O-$(C_1\text{-}C_7)$-alkyl, -O-aryl, -O-$(C_2\text{-}C_4)$-alkyl-O-$(C_1\text{-}C_7)$-alkyl, $(C_2\text{-}C_3)$-alkylenedioxy, NR^8R^9, CN, $CO\text{-}NH_2$, CO-NH-$(C_1\text{-}C_3)$-alkyl, CO-N($(C_1\text{-}C_3)$-alkyl)$_2$, COOH, CO-O-$(C_1\text{-}C_5)$-alkyl, CHO, CO-$(C_1\text{-}C_5)$-alkyl, $S(O)_n$-$(C_1\text{-}C_4)$-alkyl, $S(O)_n\text{-}NH_2$, $S(O)_n$-NH-$(C_1\text{-}C_3)$-alkyl, $S(O)_n$-N($(C_1\text{-}C_3)$-alkyl)$_2$, oxo, -$(CH_2)_m\text{-}NH_2$, -$(CH_2)_m$-NH-$(C_1\text{-}C_4)$-alkyl and -$(CH_2)_m$-N($(C_1\text{-}C_4)$-alkyl)$_2$, where in the substituent -$(CH_2)_m$-N($(C_1\text{-}C_4)$-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which in addition to the nitrogen atom and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^7 is OH, -O-$(C_1\text{-}C_7)$-alkyl, NH_2, -NH-$(C_1\text{-}C_4)$-alkyl or -N($(C_1\text{-}C_4)$-alkyl)$_2$, where in the substituent N($(C_1\text{-}C_4)$-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which, in addition to the

nitrogen atom and the carbon atoms, can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^8 is hydrogen or (C_1-C_7)-alkyl, which can be substituted by one or more identical or different substituents from the group consisting of OH, $-O-(C_1-C_5)$-alkyl, NH_2, $-NH-(C_1-C_4)$-alkyl and $-N((C_1-C_4)\text{-alkyl})_2$, where in the substituent $N((C_1-C_4)\text{-alkyl})_2$ the two alkyl groups can be linked by a single bond and then, together with the nitrogen atom carrying them, form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms, can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^9, independently of R^8, has one of the meanings of R^8 or is $CO-(C_1-C_4)$-alkyl;

aryl is phenyl, naphthyl or heteroaryl, which can all be substituted by one or more identical or different substituents from the group consisting of halogen, (C_1-C_5)-alkyl, phenyl, tolyl, CF_3, NO_2, OH, $-O-(C_1-C_5)$-alkyl, $-O-(C_2-C_4)$-alkyl-$O-(C_1-C_3)$-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, $-NH-(C_1-C_3)$-alkyl, $-N((C_1-C_3)\text{-alkyl})_2$, NH-CHO, $-NH-CO-(C_1-C_5)$-alkyl, CN, $CO-NH_2$, $CO-NH-(C_1-C_3)$-alkyl, $CO-N((C_1-C_3)\text{-alkyl})_2$, COOH, $CO-O-(C_1-C_5)$-alkyl, heterocyclyl, CHO, $CO-(C_1-C_5)$-alkyl, $S(O)_n-(C_1-C_4)$-alkyl, $S(O)_n$-phenyl, $S(O)_n$-tolyl, $S(O)_2-NH_2$, $S(O)_2-NH-(C_1-C_3)$-alkyl and $S(O)_2-N((C_1-C_3)\text{-alkyl})_2$;

heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or a bicyclic 8-membered to 10-membered aromatic heterocycle, which in each case contain one or more ring heteroatoms from the group consisting of N, O and S;

heterocyclyl is the radical of a monocyclic or polycyclic, 5-membered to 11-membered saturated or partially unsaturated heterocycle, which contains one or more ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, OH, $-O-(C_1-C_5)$-alkyl, $-O-(C_2-C_4)$-alkyl-$O-(C_1-C_3)$-alkyl, NH_2, $-NH-(C_1-C_3)$-alkyl, $-N((C_1-C_3)\text{-alkyl})_2$, CN, $CO-NH_2$, $CO-NH-(C_1-C_3)$-alkyl, $CO-N((C_1-C_3)\text{-alkyl})_2$, COOH and $CO-O-(C_1-C_5)$-alkyl;

n is 0, 1 or 2;

m is 2, 3 or 4;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts,

where compounds of the formula Ii are excluded

a) in which simultaneously A^1 is phenyl, A^2 together with the carbon atoms carrying the groups CO-NH and R^2SO_2-NH forms a benzene ring and R^1 is radicals from the group consisting of halogen, phenyloxy, naphthyloxy, 1,3-benzothiazol-2-yloxy, pyrimidin-4-yloxy and pyrimidin-6-yloxy, which can all be unsubstituted or substituted;

b) or in which A^1 or R^2 is 2,1,3-benzothiadiazol-4-yl;

c) or in which A^1 is 2-hydroxyphenyl, 2-ethoxycarbonylmethoxyphenyl, 2-carboxyphenyl, 2-carboxyalkylphenyl or 2-carbamoylphenyl;

d) or in which simultaneously the ring R^3-A^2, together with the carbon atoms carrying the groups CO-NH and R^2SO_2-NH, forms a benzene ring which is substituted in the 5-position by nitro or bromine or chlorine or is substituted in positions 5 and 6 by two chlorine atoms, R^2 is 4-chlorophenyl and A^1 is 3-trifluoromethylphenyl;

e) or in which the ring R^3-A^2, together with the carbon atoms carrying the groups CO-NH and R^2SO_2-NH, forms an indole ring on which the sulphonylamino group is in the 2-position, a 5-aminopyrazole ring on which the sulphonylamino group is in the 3-position, a 4-hydroxyquinoline ring on which the sulphonylamino group is in the 2-position, a pyrazolo[1,5-a]pyrimidine ring on which the sulphonylamino group is in the 2-position, or a cyclohexane ring;

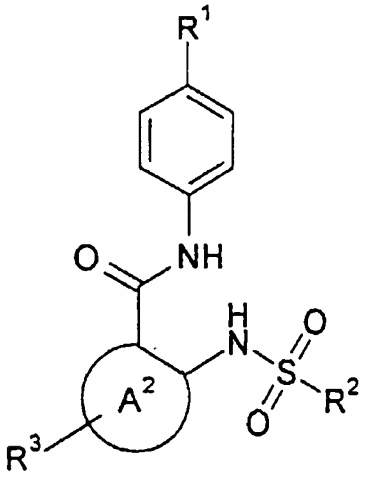
f) or in which simultaneously the ring R^3-A^2 together with the carbon atoms carrying the groups CO-NH and R^2SO_2-NH forms a benzene ring, R^2 is 4-tolyl and A^1 is 4-pyridyl.

All explanations which were given for the compounds of the formula I with the accompanying definition of the substituents given at the outset apply correspondingly to the compounds of the formula Ii with the above definition of the substituents. This is applicable, for example, to the fact that groups and substituents which occur a number of times are all independent of one another, or to all explanations for alkyl groups, aryl groups, heterocyclic radicals, possible substituents, salts, isomers, tautomers, etc. The present invention also includes all salts of the compounds of the formula Ii, which because of low physiological tolerability are not directly suitable for use in pharmaceuticals, but, for example, are suitable as intermediates for chemical syntheses or for the preparation of physiologically tolerable salts. As in the compounds of the formula I, the ring A^2 in the compounds of the formula Ii can also have, for example, the meanings shown in the formulae Ia, Ib, Ic, Id, Ie, If, Ig and Ih, if these are not excluded in the definition of the substituents in the formula Ii.

All preferred meanings of the radicals in the formula I also apply correspondingly to the radicals in the formula Ii. Likewise, preferred compounds of the formula Ii are those compounds in which one or more of the radicals have preferred meanings, where all combinations of preferred substituent definitions are a subject of the present invention. A group of preferred compounds of the formula Ii is formed, for example, of those compounds in which A^1 is phenyl which carries a radical R^1 in the 4-position; the ring A^2, which includes the carbon atoms which carry the groups CO-NH- and NH-SO_2R^2, is a benzene ring or a thiophene ring; and R^1 is a substituent from the group consisting of CO-(C_1-C_{10})-alkyl, CO-aryl, CO-NR^5R^6, -NH-CO-(C_1-C_{10})-alkyl, -NH-CO-aryl, -N(CO-(C_1-C_{10})-alkyl)$_2$, -N(CO-aryl)$_2$, -NH-SO_2-(C_1-C_{10})-alkyl, -NH-SO_2-aryl, -N(SO_2-(C_1-C_{10})-alkyl)$_2$ and –N(SO_2-aryl)$_2$, in which all alkyl radicals can be substituted by one or more identical or different radicals R^4; in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts.

Furthermore, the present invention also relates to specific compounds of the formula I as such, in which the ring A^2, which includes the carbon atoms which carry the groups CO-NH- and NH-SO_2R, carries no further substituents, that is compounds of the formula I in which R^3 is hydrogen. In

these compounds, A^1, A^2 and R^1 preferably have the meanings which are indicated above for the preferred compounds of the formula Ii. The present invention thus also relates to the compounds of the formula Ik,



Ik

in which

the ring A^2, which includes the carbon atoms which carry the groups CO-NH- and $NH-SO_2R^2$, is a benzene ring or a thiophene ring;

R^1 is a substituent from the group consisting of $CO-(C_1-C_{10})$-alkyl, CO-aryl, $CO-NR^5R^6$, $-NH-CO-(C_1-C_{10})$-alkyl, -NH-CO-aryl, $-N(CO-(C_1-C_{10})\text{-alkyl})_2$, $-N(CO\text{-aryl})_2$, $-NH-SO_2-(C_1-C_{10})$-alkyl, $-NH-SO_2$-aryl, $-N(SO_2-(C_1-C_{10})\text{-alkyl})_2$ and $-N(SO_2\text{-aryl})_2$, in which all alkyl radicals can be substituted by one or more identical or different radicals R^4;

R^2 is aryl, heterocyclyl or NR^5R^6;

R^3 is one or more identical or different substituents from the group consisting of hydrogen, halogen, CF_3, OH, $-O-(C_1-C_{10})$-alkyl, $-O-(C_1-C_7)\text{-alkyl-}R^7$, -O-aryl, SH, $-S-(C_1-C_{10})$-alkyl, $-S-(C_1-C_7)\text{-alkyl-}R^7$, -S-aryl, (C_1-C_2)-alkylenedioxy, CN, NO_2, NR^8R^9, $CO-NR^5R^6$, COOH, $CO-O-(C_1-C_5)$-alkyl, heterocyclyl, $S(O)_n-(C_1-C_7)$-alkyl, $S(O)_n$-aryl, $S(O)_n-NR^5R^6$ and (C_1-C_7)-alkyl which can be substituted by one or more identical or different radicals R^4;

R^4 is fluorine, OH, $-O-(C_1-C_{10})$-alkyl, $-O-(C_1-C_7)\text{-alkyl-}R^7$, -O-aryl, SH, $-S-(C_1-C_{10})$-alkyl, $-S-(C_1-C_7)\text{-alkyl-}R^7$, -S-aryl, $-P(O)(O-(C_1-C_5)\text{-alkyl})_2$, -P(O)-

$(OH)_2$, CN, NR^8R^9, $CO\text{-}NH_2$, $CO\text{-}NH\text{-}(C_1\text{-}C_3)$-alkyl, $CO\text{-}N((C_1\text{-}C_3)\text{-alkyl})_2$, COOH, $CO\text{-}O\text{-}(C_1\text{-}C_5)$-alkyl, heterocyclyl or oxo;

R^5 is hydrogen, $(C_1\text{-}C_{10})$-alkyl which can be substituted by one or more identical or different substituents R^4 and/or by aryl, or is aryl, heterocyclyl, CO- $(C_1\text{-}C_{10})$-alkyl, CO-aryl, CO-heterocyclyl, $SO_2\text{-}(C_1\text{-}C_{10})$-alkyl, SO_2-aryl or SO_2-heterocyclyl;

R^6, independently of R^5, has one of the meanings indicated for R^5, or R^5 and R^6, together with the nitrogen atom to which they are bonded, form a 5-membered to 8-membered saturated or partially unsaturated ring, which in addition to the nitrogen atom carrying the groups R^5 and R^6 can also contain one or more further ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, $(C_1\text{-}C_5)$-alkyl, $(C_1\text{-}C_3)$-hydroxyalkyl, $\text{-}(C_1\text{-}C_3)\text{-alkyl-O-}(C_1\text{-}C_4)$-alkyl, aryl, CF_3, OH, $\text{-O-}(C_1\text{-}C_7)$-alkyl, -O-aryl, $\text{-O-}(C_2\text{-}C_4)\text{-alkyl-O-}(C_1\text{-}C_7)$-alkyl, $(C_2\text{-}C_3)$-alkylenedioxy, NR^8R^9, CN, $CO\text{-}NH_2$, $CO\text{-}NH\text{-}(C_1\text{-}C_3)$-alkyl, $CO\text{-}N((C_1\text{-}C_3)\text{-alkyl})_2$, COOH, $CO\text{-}O\text{-}(C_1\text{-}C_5)$-alkyl, CHO, $CO\text{-}(C_1\text{-}C_5)$-alkyl, $S(O)_n\text{-}(C_1\text{-}C_4)$-alkyl, $S(O)_n\text{-}NH_2$, $S(O)_n\text{-}NH\text{-}(C_1\text{-}C_3)$-alkyl, $S(O)_n\text{-}N((C_1\text{-}C_3)\text{-alkyl})_2$, oxo, $\text{-}(CH_2)_m\text{-}NH_2$, $\text{-}(CH_2)_m\text{-}NH\text{-}(C_1\text{-}C_4)$-alkyl and $\text{-}(CH_2)_m\text{-}N((C_1\text{-}C_4)\text{-alkyl})_2$, where in the substituent $\text{-}(CH_2)_m\text{-}N((C_1\text{-}C_4)\text{-alkyl})_2$ the two alkyl groups can be linked by a single bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which in addition to the nitrogen atom and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^7 is OH, $\text{-O-}(C_1\text{-}C_7)$-alkyl, NH_2, $\text{-NH-}(C_1\text{-}C_4)$-alkyl or $\text{-N}((C_1\text{-}C_4)\text{-alkyl})_2$, where in the substituent $N((C_1\text{-}C_4)\text{-alkyl})_2$ the two alkyl groups can be linked by a single bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which in addition to the nitrogen atom and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^8 is hydrogen or $(C_1\text{-}C_7)$-alkyl, which can be substituted by one or more identical or different substituents from the group consisting of OH, $\text{-O-}(C_1\text{-}C_5)$-alkyl, NH_2, $\text{-NH-}(C_1\text{-}C_4)$-alkyl and $\text{-N}((C_1\text{-}C_4)\text{-alkyl})_2$, where in the substituent $N((C_1\text{-}C_4)\text{-alkyl})_2$ the two alkyl groups can be linked by a single

bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which in addition to the nitrogen atom and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^9, independently of R^8, has one of the meanings of R^8 or is CO-(C_1-C_4)-alkyl;

aryl is phenyl, naphthyl or heteroaryl, which can all be substituted by one or more identical or different substituents from the group consisting of halogen, (C_1-C_5)-alkyl, phenyl, tolyl, CF_3, NO_2, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_3)-alkyl, -N((C_1-C_3)-alkyl)$_2$, NH-CHO, -NH-CO-(C_1-C_5)-alkyl, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_5)-alkyl, S(O)$_n$-(C_1-C_4)-alkyl, S(O)$_n$-phenyl, S(O)$_n$-tolyl, S(O)$_2$-NH_2, S(O)$_2$-NH-(C_1-C_3)-alkyl and S(O)$_2$-N((C_1-C_3)-alkyl)$_2$;

heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle which in each case contain one or more ring heteroatoms from the group consisting of N, O and S;

heterocyclyl is the radical of a monocyclic or polycyclic, 5-membered to 11-membered saturated or partially unsaturated heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, NH_2, -NH-(C_1-C_3)-alkyl, -N((C_1-C_3)-alkyl)$_2$, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH and CO-O-(C_1-C_5)-alkyl;

n is 0, 1 or 2;

m is 2, 3 or 4;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts.

All explanations which were given for the compounds of the formula I having the associated definition of the substituents given at the outset also apply, if applicable, correspondingly to the compounds of the formula Ik having the above definition of the substituents. This applies, for example, to the fact that groups and substituents which occur a number of times are all independent of one another, or to all explanations for alkyl groups, aryl groups, heterocyclic radicals, possible substituents, salts, isomers, tautomers, etc. The present invention also includes all salts of the compounds of the formula Ik which, because of low physiological tolerability, are not directly suitable for use in pharmaceuticals, but are suitable, for example, as intermediates for chemical syntheses or for the production of physiologically tolerable salts. As in the compounds of the formula I, the ring A^2 in the compounds of the formula Ik can also, for example, have the meanings shown in the formulae Ia, If, Ig and Ih. All preferred meanings of the radicals in the formula I also apply correspondingly to the radicals in the formula Ik. Likewise, preferred compounds of the formula Ik are those compounds in which one or more of the radicals have preferred meanings, where all combinations of preferred substituent definitions are a subject of the present invention.

Furthermore, the above details for the preparation of the compounds of the formula I and for their biological properties and for their use, and for pharmaceutical preparations comprising them naturally also apply to the compounds of the formulae Ii and Ik. The present invention also relates to processes for the preparation of the compounds of the formulae Ii and Ik defined above by the synthesis process described above, the compounds of the formulae Ii and Ik and their physiologically tolerable salts for use as pharmaceuticals and pharmaceutical preparations which contain an efficacious dose of at least one compound of the formulae Ii or Ik or of a physiologically tolerable salt thereof as active constituent in addition to customary pharmaceutically innocuous vehicles and/or additives.

The following example compounds, which were prepared according to or analogously to processes described in the literature, illustrate the invention without restricting it.

Examples

1) 2-(4-Chlorophenylsulphonylamino)-N-(3-trifluoromethylphenyl)-benzamide
M.p.: 169°C

2) 5-Bromo-2-(4-chlorophenylsulphonylamino)-N-(3-trifluoromethyl-phenyl)benzamide
M.p.: 220°C

3) 2-(4-Chlorophenylsulphonylamino)-N-(2-naphthyl)benzamide
M.p.: 189°C

4) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-trifluoromethyl-phenyl)benzamide
M.p.: 216°C

5) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-phenoxyphenyl)-benzamide
M.p.: 205°C

6) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-(4-chlorophenoxy)-phenyl)benzamide
M.p.: 207°C

7) 2-(4-Chlorophenylsulphonylamino)-N-(4-phenoxyphenyl)benzamide
M.p.: 143°C

8) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3,4-dichlorophenyl)-benzamide
M.p.: 244°C

9) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-bromophenyl)-benzamide
M.p.: 210°C

10) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-chlorophenyl)-benzamide
M.p.: 228°C

11) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-methoxyphenyl)-benzamide
M.p.: 190°C

12) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-naphthyl)benzamide
M.p.: 211°C

13) 5-Chloro-2-(4-fluorophenylsulphonylamino)-N-(3,5-dichlorophenyl)-benzamide
M.p.: 250°C

14) Ethyl 4-(5-chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-benzoate
M.p.: 185°

15) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-(bismethylsulphonylamino)phenyl)benzamide
M.p.: 235°C

16) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-isopropylphenyl)-benzamide
M.p.: 188°C

17) 5-Chloro-2-(3-chloro-4-methoxyphenylsulphonylamino)-N-(4-fluoro-phenyl)benzamide
M.p.: 188°C

18) Ethyl 2-chloro-5-(5-chloro-2-(3,4-dichlorophenylsulphonylamino)-benzoylamino)benzoate
M.p.: 202°C

19) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-chloro-4-(4-chloro-naphthalene-1-yloxy)phenyl)benzamide

20) 2-(4-Chlorophenylsulphonylamino)-5-chloro-N-(4-tert-butylphenyl)-benzamide
M.p.: 91°C

21) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-(morpholin-4-yl)-phenyl)benzamide
M.p.: 228.5°C

22) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-(phenylamino)-phenyl)benzamide
M.p.: 192.5°C

23) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-(benzyloxy)phenyl)-benzamide
M.p.: 191°C

24) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-acetylphenyl)-benzamide
M.p.: 226°C

25) 2-Phenylsulphonylamino-5-chloro-N-(4-(2-oxopyrrolidin-1-yl)phenyl)-benzamide
M.p.: 218°C

26) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(5-methylpyrazin-3-yl)-benzamide
M.p.: 248°C

27) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-(2-thienyl)pyrazol-5-yl)benzamide
M.p.:117°C

28) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3,5-bis-trifluoromethylphenyl)benzamide
M.p.: 182.5°C

29) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-methoxy-5-trifluoromethylphenyl)benzamide
M.p.: 164.5°C

30) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-trifluoromethyl-phenyl)benzamide

M.p.: 182°C

31) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-methoxyphenyl)-benzamide
M.p.: 163.5°C

32) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3,5-dimethoxyphenyl)-benzamide
M.p.: 74.5°C

33) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-(morpholine-4-carbonyl)phenyl)benzamide

34) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-(2,5-dioxopyrrolidin-1-yl)phenyl)benzamide

35) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(1H-indol-5-yl)-benzamide

36) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(quinolin-8-yl)-benzamide

37) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-methyl-2-oxo-2H-chromen-7-yl)benzamide

38) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(isoquinolin-5-yl)-benzamide

39) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-ethoxy-2-nitro-phenyl)benzamide

40) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-methoxy-5-nitro-phenyl)benzamide

41) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2,5-dimethoxy-4-nitrophenyl)benzamide

42) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-methoxy-4-nitro-phenyl)benzamide

43) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-cyanophenyl)-benzamide

44) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-cyano-2,3,5,6-tetrafluorophenyl)benzamide

45) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-(2-hydroxyethyl)-phenyl)benzamide

46) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-cyanophenyl)-benzamide

47) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-benzoylamino-5-chloro-2-methylphenyl)benzamide

48) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-(1-hydroxyethyl)-phenyl)benzamide

49) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-cyanophenyl)-benzamide

50) N-(2-Benzoyl-4-chlorophenyl)-5-chloro-2-(4-chlorophenylsulphonyl-amino)benzamide

51) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-diethylaminophenyl)benzamide

52) N-(4-Butoxyphenyl)-5-chloro-2-(4-chlorophenylsulphonylamino)-benzamide

53) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-hexyloxyphenyl)-benzamide

54) Diethyl (4-(5-chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-benzyl)phosphonate

55) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-pentylphenyl)-benzamide

56) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3,4,5-trimethoxyphenyl)benzamide

57) Diethyl 2-(4-(5-chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)benzoylamino)pentanedioate

58) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-methoxydibenzofuran-3-yl)benzamide

59) Butyl 4-(5-chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)benzoate

60) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-phenoxyphenyl)benzamide

61) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-phenoxyphenyl)benzamide

62) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-hydroxybiphenyl-3-yl)benzamide

63) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-hydroxy-2-nitrophenyl)benzamide

64) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-hydroxymethyl-2-methylphenyl)benzamide

65) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(5-hydroxymethyl-2-methylphenyl)benzamide

66) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-(4-methylphenylsulphonylamino)phenyl)benzamide

67) 2-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)benzoic acid

68) tert-Butyl-(4-(5-chloro-2-(4-chlorophenylsulphonylamino)-benzoylamino)phenyl)carbamate

69) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3,4,5-trifluorophenyl)-benzamide

70) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)benzamide

71) 3-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)benzoic acid

72) 2-Diethylaminoethyl 4-(5-chloro-2-(4-chlorophenylsulphonylamino)-benzoylamino)benzoate

73) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-oxo-4-trifluoromethyl-2H-chromen-7-yl)benzamide

74) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-hydroxymethyl-4-methylphenyl)benzamide

75) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-(pyrrol-1-yl)-phenyl)benzamide

76) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)benzamide

77) Ethyl 3-(5-chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-benzoate

78) N-(Benzo[1,3]dioxol-5-yl)-5-chloro-2-(4-chlorophenylsulphonylamino)- benzamide

79) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-chloro-4-cyano-phenyl)-benzamide

80) Methyl 2-(5-chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-4,5-dimethoxybenzoate

81) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-nitrophenyl)-benzamide

82) Methyl 3-(5-chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-benzoate

83) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-(morpholin-4-yl)-5-trifluoromethylphenyl)benzamide

84) N-(1H-Benzotriazol-5-yl)-5-chloro-2-(4-chlorophenylsulphonylamino)benzamide

85) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-methoxymethyl-2-oxo-2H-chromen-7-yl)benzamide

86) N-(2-(1H-Benzimidazol-2-yl)phenyl)-5-chloro-2-(4-chlorophenyl-sulphonylamino)benzamide

87) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-(N-phenyl-carbamoyl)phenyl)benzamide

88) N-(3-Benzoylphenyl)-5-chloro-2-(4-chlorophenylsulphonylamino)-benzamide

89) Methyl 4-(5-chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-2-methoxybenzoate

90) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-carbamoylphenyl)-benzamide

91) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-carbamoylphenyl)-benzamide

92) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-carbamoyl-2-methoxyphenyl)benzamide

93) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(3-diethylaminomethyl-4-hydroxyphenyl)benzamide

94) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2,5-diethoxy-4-(morpholin-4-yl)phenyl)benzamide

95) N-(3-Acetylaminophenyl)-5-chloro-2-(4-chlorophenylsulphonylamino)benzamide

96) 3-(4-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-phenyl)acrylic acid

97) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(4-(cyanophenyl-methyl)phenyl)benzamide

98) 5-Chloro-2-4-chlorophenylsulphonylamino)-N-(4-(ethyl(2-hydroxy-ethyl)amino)phenyl)benzamide

99) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-(2,4-dichloro-phenoxy)phenyl)benzamide

100) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(2-oxo-2H-chromen-6-yl)benzamide

101) N-(4-(5-chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-phenyl)oxamide

102) (4-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-benzoylamino)acetic acid

103) (4-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-phenyl)acetic acid

104) 3-(4-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-benzoylamino)propionic acid

105) (4-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-benzyl)phosphonic acid

106) 4-(4-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-phenyl)butyric acid

107) 2-(4-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-benzoylamino)pentanedioic acid

108) (3-(5-Chloro-2-(4-chlorophenylsulphonylamino)benzoylamino)-phenyl)acetic acid

109) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(1H-indazol-6-yl))-benzamide

110) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(quinolin-5-yl)-benzamide

111) 5-Chloro-2-(4-chlorophenylsulphonylamino)-N-(quinolin-6-yl)-benzamide

Pharmacological investigations

1) Activation of soluble guanylate cyclase

The activation of soluble guanylate cyclase (sGC), which catalyses the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) and pyrophosphate, by the compounds according to the invention was quantified with the aid of an enzyme immunoassay (EIA) from Amersham. For this, the test substances were first incubated with sGC in microtiter plates and then the quantity of the resulting cGMP was determined.

The sGC employed had been isolated from bovine lung (see Methods in Enzymology, Volume 195, p. 377). The test solutions (100 µl per well) contained 50 mM triethanolamine (TEA) buffer (pH 7.5), 3 mM $MgCl_2$, 3 mM reduced glutathione (GSH), 0.1 mM GTP, 1 mM 3-isobutyl-1-methylxanthine (IBMX), suitably diluted enzyme solution and the test substance or, in the control experiments, solvent. The test substances were dissolved in dimethyl sulfoxide (DMSO) and the solution was diluted with DMSO/water such that the final concentration c of test substance in the test batch had the value indicated below. The DMSO concentration in the test batch was 5% (v/v). The reaction was started by addition of the sGC. The reaction mix was incubated at 37°C for 15 to 20 minutes and then stopped by ice-cooling and addition of the stop reagent (50 mM EDTA, pH 8.0). An aliquot of 50 µl was taken and employed for the determination of the cGMP content using the acetylation protocol of the Amersham cGMP EIA kit. The

absorption of the samples was measured at 450 nm (reference wavelength 620 nm) in a microtiter plate-reading apparatus. The cGMP concentration was determined by means of a calibration curve, which was obtained under the same experimental conditions. The activation of the sGC by a test substance is indicated as n-fold stimulation of the basal enzyme activity which was found in the control experiments (with solvent instead of test substance) (calculated according to the formula
n-fold stimulation = $[cGMP]_{test\ substance}$ / $[cGMP]_{control}$).

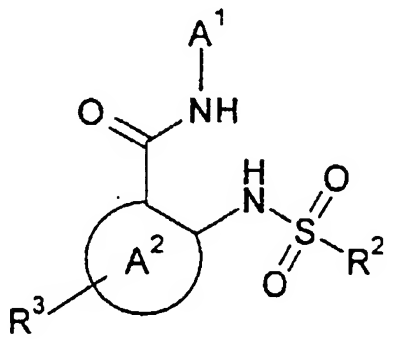
The following results were obtained:

Compound of Example No.	Concentration c (μM)	n-fold stimulation
1	100	3.6
2	100	9.2
3	100	2
4	25	5.5
5	10	9.3
6	100	4.2
7	100	2.8
8	10	5.3
9	100	1.6
10	100	1.7
11	100	1.8
12	25	2.8
13	100	1.8
14	100	1.7
15	10	9.9
16	100	4.1
17	100	2
18	100	3.2
19	100	26.3
21	50	8
23	25	2.2
24	50	2.4
25	50	2.4
33	50	3.8
93	50	1.5

97	12.5	4.9
102	50	1.7
108	50	2.5
111	50	6.1

Patent Claims

1. The use of compounds of the formula I



I

in which

A^1 is a radical from the group consisting of phenyl, naphthyl and heteroaryl, which can all be substituted by one or more identical or different radicals R^1;

the ring A^2, which includes the carbon atoms which carry the groups CO-NH- and NH-SO_2R^2, is a benzene ring, a naphthalene ring, a saturated or partially unsaturated 3-membered to 7-membered carbocycle, a saturated, partially unsaturated or aromatic monocyclic 5-membered to 7-membered heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S, or a saturated, partially unsaturated or aromatic bicyclic 8-membered to 10-membered heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S;

R^1 is halogen, aryl, CF_3, NO_2, OH, -O-(C_1-C_7)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, -O-aryl, (C_1-C_2)-alkylenedioxy, NR^5R^6, CN, CO-NR^5R^6, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_{10})-alkyl, CO-aryl or (C_1-C_{10})-alkyl which can be substituted by one or more identical or different radicals R^4;

R^2 is aryl, heterocyclyl, NR^5R^6 or (C_1-C_{10})-alkyl which can be substituted by one or more identical or different radicals R^4;

R^3 is one or more identical or different substituents from the group consisting of hydrogen, halogen, CF_3, OH, -O-(C_1-C_{10})-alkyl, -O-(C_1-C_7)-

alkyl-R^7, -O-aryl, SH, -S-(C_1-C_{10})-alkyl, -S-(C_1-C_7)-alkyl-R^7, -S-aryl, (C_1-C_3)-alkylenedioxy, CN, NO_2, NR^8R^9, CO-NR^5R^6, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, $S(O)_n$-(C_1-C_7)-alkyl, $S(O)_n$-aryl, $S(O)_n$-NR^5R^6 and (C_1-C_7)-alkyl which can be substituted by one or more identical or different radicals R^4;

R^4 is fluorine, OH, -O-(C_1-C_{10})-alkyl, -O-(C_1-C_7)-alkyl-R^7, -O-aryl, SH, -S-(C_1-C_{10})-alkyl, -S-(C_1-C_7)-alkyl-R^7, -S-aryl, -P(O)(O-(C_1-C_5)-alkyl)$_2$, -P(O)-(OH)$_2$, CN, NR^8R^9, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl or oxo;

R^5 is hydrogen, (C_1-C_{10})-alkyl which can be substituted by one or more identical or different substituents R^4 and/or by aryl, or is aryl, heterocyclyl, CO- (C_1-C_{10})-alkyl, CO-aryl, CO-heterocyclyl, SO_2-(C_1-C_{10})-alkyl, SO_2-aryl or SO_2-heterocyclyl;

R^6, independently of R^5, has one of the meanings indicated for R^5, or R^5 and R^6, together with the nitrogen atom to which they are bonded, form a 5-membered to 8-membered saturated or partially unsaturated ring which, in addition to the nitrogen atom carrying the groups R^5 and R^6, can also contain one or more further ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, (C_1-C_3)-hydroxyalkyl, -(C_1-C_3)-alkyl-O-(C_1-C_4)-alkyl, aryl, CF_3, OH, -O-(C_1-C_7)-alkyl, -O-aryl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, (C_2-C_3)-alkylenedioxy, NR^8R^9, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, CHO, CO-(C_1-C_5)-alkyl, $S(O)_n$-(C_1-C_4)-alkyl, $S(O)_n$-NH_2, $S(O)_n$-NH-(C_1-C_3)-alkyl, $S(O)_n$-N((C_1-C_3)-alkyl)$_2$, oxo, -$(CH_2)_m$-NH_2, -$(CH_2)_m$-NH-(C_1-C_4)-alkyl and –$(CH_2)_m$-N((C_1-C_4)-alkyl)$_2$, where in the substituent -$(CH_2)_m$-N((C_1-C_4)-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then, together with the nitrogen atom carrying them, form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms, can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^7 is OH, -O-(C_1-C_7)-alkyl, NH_2, -NH-(C_1-C_4)-alkyl or -N((C_1-C_4)-alkyl)$_2$, where in the substituent N((C_1-C_4)-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then, together with the nitrogen atom carrying

them, form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^8 is hydrogen or (C_1-C_7)-alkyl which can be substituted by one or more identical or different substituents from the group consisting of OH, -O-(C_1-C_5)-alkyl, NH_2, -NH-(C_1-C_4)-alkyl and –N((C_1-C_4)-alkyl)$_2$;

R^9, independently of R^8, has one of the meanings of R^8 or is CO-(C_1-C_4)-alkyl;

aryl is phenyl, naphthyl or heteroaryl, which can all be substituted by one or more identical or different substituents from the group consisting of halogen, (C_1-C_5)-alkyl, phenyl, tolyl, CF_3, NO_2, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_3)-alkyl, -N((C_1-C_3)-alkyl)$_2$, NH-CHO, -NH-CO-(C_1-C_5)-alkyl, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_5)-alkyl, S(O)$_n$-(C_1-C_4)-alkyl, S(O)$_n$-phenyl, S(O)$_n$-tolyl, $S(O)_2-NH_2$, $S(O)_2$-NH-(C_1-C_3)-alkyl and $S(O)_2$-N((C_1-C_3)-alkyl)$_2$;

heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle, each of which contain one or more ring heteroatoms from the group consisting of N, O and S;

heterocyclyl is the radical of a monocyclic or polycyclic, 5-membered to 11-membered saturated or partially unsaturated heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, NH_2, -NH-(C_1-C_3)-alkyl, -N((C_1-C_3)-alkyl)$_2$, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH and CO-O-(C_1-C_5)-alkyl;

n is 0, 1 or 2;

m is 2, 3 or 4;

in all their stereoisomeric forms and mixtures thereof in all ratios, and/or their physiologically tolerable salts for the production of a medicament for the activation of soluble guanylate cyclase.

2. The use of compounds of the formula I as claimed in claim 1 and/or their physiologically tolerable salts, in which A^1 is phenyl, naphthyl or bicyclic heteroaryl, where these radicals can be unsubstituted or substituted.

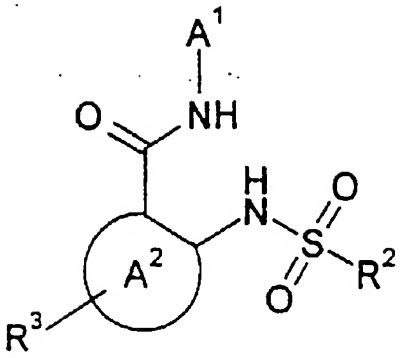
3. The use of compounds of the formula I as claimed in claim 1 and/or 2 and/or their physiologically tolerable salts, in which A^2 together with the atoms carrying both the group R^2-SO_2-NH and the group CO-NH forms an aromatic ring.

4. The use of compounds of the formula I as claimed in one or more of claims 1 to 3 and/or their physiologically tolerable salts, in which R^2 is unsubstituted or substituted aryl.

5. The use of compounds of the formula I as claimed in one or more of claims 1 to 4 and/or their physiologically tolerable salts, in which A^2 together with the atoms carrying both the group R^2-SO_2-NH and the group CO-NH forms an unsubstituted or substituted benzene ring and R^2 is unsubstituted or substituted aryl.

6. The use of compounds of the formula I as claimed in one or more of claims 1 to 5 and/or their physiologically tolerable salts for the production of a medicament for the therapy or prophylaxis of cardiovascular disorders, endothelial dysfunction, diastolic dysfunction, atherosclerosis, high blood pressure, angina pectoris, thromboses, restenoses, myocardial infarct, strokes, cardiac insufficiency, pulmonary hypertension, erectile dysfunction, bronchial asthma, chronic renal insufficiency, diabetes or liver cirrhosis or for improving a restricted learning capacity or memory power.

7. A compound of the formula Ii



Ii

in which

A^1 is a radical from the group consisting of phenyl, naphthyl and heteroaryl, which can all be substituted by one or more identical or different radicals R^1;

the ring A^2, which includes the carbon atoms which carry the groups CO-NH- and NH-SO_2R^2, is a benzene ring, a naphthalene ring, a saturated or partially unsaturated 3-membered to 7-membered carbocycle, a saturated, partially unsaturated or aromatic monocyclic 5-membered to 7-membered heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S, or a saturated, partially unsaturated or aromatic bicyclic 8-membered to 10-membered heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S;

R^1 is halogen, aryl, CF_3, NO_2, OH, -O-(C_1-C_7)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, -O-aryl, (C_1-C_2)-alkylenedioxy, NR^5R^6, CN, CO-NR^5R^6, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_{10})-alkyl, CO-aryl or (C_1-C_{10})-alkyl which can be substituted by one or more identical or different radicals R^4;

R^2 is aryl, heterocyclyl, NR^5R^6;

R^3 is one or more identical or different substituents from the group consisting of halogen, CF_3, OH, -O-(C_1-C_{10})-alkyl, -O-(C_1-C_7)-alkyl-R^7, -O-aryl, SH, -S-(C_1-C_{10})-alkyl, -S-(C_1-C_7)-alkyl-R^7, -S-aryl, (C_1-C_3)-alkylenedioxy, CN, NO_2, NR^8R^9, CO-NR^5R^6, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, $S(O)_n$-(C_1-C_7)-alkyl, $S(O)_n$-aryl, $S(O)_n$-NR^5R^6 and (C_1-C_7)-

alkyl which can be substituted by one or more identical or different radicals R^4;

R^4 is fluorine, OH, -O-(C_1-C_{10})-alkyl, -O-(C_1-C_7)-alkyl-R^7, -O-aryl, SH, -S-(C_1-C_{10})-alkyl, -S-(C_1-C_7)-alkyl-R^7, -S-aryl, -P(O)(O-(C_1-C_5)-alkyl)$_2$, -P(O)-(OH)$_2$, CN, NR^8R^9, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl or oxo;

R^5 is hydrogen, (C_1-C_{10})-alkyl which can be substituted by one or more identical or different substituents R^4 and/or by aryl, or is aryl, heterocyclyl, CO- (C_1-C_{10})-alkyl, CO-aryl, CO-heterocyclyl, SO_2-(C_1-C_{10})-alkyl, SO_2-aryl or SO_2-heterocyclyl;

R^6, independently of R^5, has one of the meanings indicated for R^5, or R^5 and R^6, together with the nitrogen atom to which they are bonded, form a 5-membered to 8-membered saturated or partially unsaturated ring which, in addition to the nitrogen atom carrying the groups R^5 and R^6 can also contain one or more further ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, (C_1-C_3)-hydroxyalkyl, -(C_1-C_3)-alkyl-O-(C_1-C_4)-alkyl, aryl, CF_3, OH, -O-(C_1-C_7)-alkyl, -O-aryl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, (C_2-C_3)-alkylenedioxy, NR^8R^9, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, CHO, CO-(C_1-C_5)-alkyl, S(O)$_n$-(C_1-C_4)-alkyl, S(O)$_n$-NH_2, S(O)$_n$-NH-(C_1-C_3)-alkyl, S(O)$_n$-N((C_1-C_3)-alkyl)$_2$, oxo, -(CH_2)$_m$-NH_2, -(CH_2)$_m$-NH-(C_1-C_4)-alkyl and -(CH_2)$_m$-N((C_1-C_4)-alkyl)$_2$, where in the substituent -(CH_2)$_m$-N((C_1-C_4)-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which in addition to the nitrogen atom and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^7 is OH, -O-(C_1-C_7)-alkyl, NH_2, -NH-(C_1-C_4)-alkyl or -N((C_1-C_4)-alkyl)$_2$, where in the substituent N((C_1-C_4)-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms, can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^8 is hydrogen or $(C_1$-$C_7)$-alkyl which can be substituted by one or more identical or different substituents from the group consisting of OH, -O-$(C_1$-$C_5)$-alkyl, NH_2, -NH-$(C_1$-$C_4)$-alkyl and -N$((C_1$-$C_4)$-alkyl$)_2$, where in the substituent N$((C_1$-$C_4)$-alkyl$)_2$ the two alkyl groups can be linked by a single bond and then, together with the nitrogen atom carrying them, form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms, can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^9, independently of R^8, has one of the meanings of R^8 or is CO-$(C_1$-$C_4)$-alkyl;

aryl is phenyl, naphthyl or heteroaryl, which can all be substituted by one or more identical or different substituents from the group consisting of halogen, $(C_1$-$C_5)$-alkyl, phenyl, tolyl, CF_3, NO_2, OH, -O-$(C_1$-$C_5)$-alkyl, -O-$(C_2$-$C_4)$-alkyl-O-$(C_1$-$C_3)$-alkyl, $(C_1$-$C_2)$-alkylenedioxy, NH_2, -NH-$(C_1$-$C_3)$-alkyl, -N$((C_1$-$C_3)$-alkyl$)_2$, NH-CHO, -NH-CO-$(C_1$-$C_5)$-alkyl, CN, CO-NH_2, CO-NH-$(C_1$-$C_3)$-alkyl, CO-N$((C_1$-$C_3)$-alkyl$)_2$, COOH, CO-O-$(C_1$-$C_5)$-alkyl, heterocyclyl, CHO, CO-$(C_1$-$C_5)$-alkyl, $S(O)_n$-$(C_1$-$C_4)$-alkyl, $S(O)_n$-phenyl, $S(O)_n$-tolyl, $S(O)_2$-NH_2, $S(O)_2$-NH-$(C_1$-$C_3)$-alkyl and $S(O)_2$-N$((C_1$-$C_3)$-alkyl$)_2$;

heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or a bicyclic 8-membered to 10-membered aromatic heterocycle, which in each case contain one or more ring heteroatoms from the group consisting of N, O and S;

heterocyclyl is the radical of a monocyclic or polycyclic, 5-membered to 11-membered saturated or partially unsaturated heterocycle, which contains one or more ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, $(C_1$-$C_5)$-alkyl, OH, -O-$(C_1$-$C_5)$-alkyl, -O-$(C_2$-$C_4)$-alkyl-O-$(C_1$-$C_3)$-alkyl, NH_2, -NH-$(C_1$-$C_3)$-alkyl, -N$((C_1$-$C_3)$-alkyl$)_2$, CN, CO-NH_2, CO-NH-$(C_1$-$C_3)$-alkyl, CO-N$((C_1$-$C_3)$-alkyl$)_2$, COOH and CO-O-$(C_1$-$C_5)$-alkyl;

n is 0, 1 or 2;

m is 2, 3 or 4;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts,

where compounds of the formula Ii are excluded

a) in which simultaneously A^1 is phenyl, A^2 together with the carbon atoms carrying the groups CO-NH and R^2SO_2-NH forms a benzene ring and R^1 is radicals from the group consisting of halogen, phenyloxy, naphthyloxy, 1,3-benzothiazol-2-yloxy, pyrimidin-4-yloxy and pyrimidin-6-yloxy, which can all be unsubstituted or substituted;

b) or in which A^1 or R^2 is 2,1,3-benzothiadiazol-4-yl;

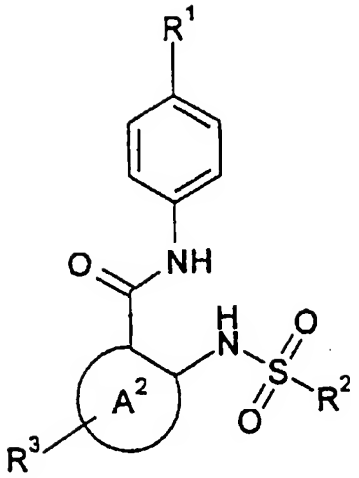
c) or in which A^1 is 2-hydroxyphenyl, 2-ethoxycarbonylmethoxyphenyl, 2-carboxyphenyl, 2-carboxyalkylphenyl or 2-carbamoylphenyl;

d) or in which simultaneously the ring R^3-A^2 together with the carbon atoms carrying the groups CO-NH and R^2SO_2-NH forms a benzene ring which is substituted in the 5-position by nitro or bromine or chlorine or is substituted in positions 5 and 6 by two chlorine atoms, R^2 is 4-chlorophenyl and A^1 is 3-trifluoromethylphenyl;

e) or in which the ring R^3-A^2, together with the carbon atoms carrying the groups CO-NH and R^2SO_2-NH, forms an indole ring on which the sulphonylamino group is in the 2-position, a 5-aminopyrazole ring on which the sulphonylamino group is in the 3-position, a 4-hydroxyquinoline ring on which the sulphonylamino group is in the 2-position, a pyrazolo[1,5-a]pyrimidine ring on which the sulphonylamino group is in the 2-position, or a cyclohexane ring;

f) or in which simultaneously the ring R^3-A^2 together with the carbon atoms carrying the groups CO-NH and R^2SO_2-NH forms a benzene ring, R^2 is 4-tolyl and A^1 is 4-pyridyl.

8. A compound of the formula Ik



Ik

in which

the ring A^2, which includes the carbon atoms which carry the groups CO-NH- and $NH-SO_2R^2$, is a benzene ring or a thiophene ring;

R^1 is a substituent from the group consisting of $CO-(C_1-C_{10})$-alkyl, CO-aryl, $CO-NR^5R^6$, $-NH-CO-(C_1-C_{10})$-alkyl, -NH-CO-aryl, $-N(CO-(C_1-C_{10})-alkyl)_2$, $-N(CO-aryl)_2$, $-NH-SO_2-(C_1-C_{10})$-alkyl, $-NH-SO_2$-aryl, $-N(SO_2-(C_1-C_{10})-alkyl)_2$ and $-N(SO_2-aryl)_2$, in which all alkyl radicals can be substituted by one or more identical or different radicals R^4;

R^2 is aryl, heterocyclyl or NR^5R^6;

R^3 is one or more identical or different substituents from the group consisting of hydrogen, halogen, CF_3, OH, $-O-(C_1-C_{10})$-alkyl, $-O-(C_1-C_7)-alkyl-R^7$, -O-aryl, SH, $-S-(C_1-C_{10})$-alkyl, $-S-(C_1-C_7)-alkyl-R^7$, -S-aryl, (C_1-C_2)-alkylenedioxy, CN, NO_2, NR^8R^9, $CO-NR^5R^6$, COOH, $CO-O-(C_1-C_5)$-alkyl, heterocyclyl, $S(O)_n-(C_1-C_7)$-alkyl, $S(O)_n$-aryl, $S(O)_n-NR^5R^6$ and (C_1-C_7)-alkyl which can be substituted by one or more identical or different radicals R^4;

R^4 is fluorine, OH, $-O-(C_1-C_{10})$-alkyl, $-O-(C_1-C_7)-alkyl-R^7$, -O-aryl, SH, $-S-(C_1-C_{10})$-alkyl, $-S-(C_1-C_7)-alkyl-R^7$, -S-aryl, $-P(O)(O-(C_1-C_5)-alkyl)_2$, $-P(O)-(OH)_2$, CN, NR^8R^9, $CO-NH_2$, $CO-NH-(C_1-C_3)$-alkyl, $CO-N((C_1-C_3)-alkyl)_2$, COOH, $CO-O-(C_1-C_5)$-alkyl, heterocyclyl or oxo;

R^5 is hydrogen, (C_1-C_{10})-alkyl which can be substituted by one or more identical or different substituents R^4 and/or by aryl, or is aryl, heterocyclyl, CO- (C_1-C_{10})-alkyl, CO-aryl, CO-heterocyclyl, SO_2-(C_1-C_{10})-alkyl, SO_2-aryl or SO_2-heterocyclyl;

R^6, independently of R^5, has one of the meanings indicated for R^5, or R^5 and R^6, together with the nitrogen atom to which they are bonded, form a 5-membered to 8-membered saturated or partially unsaturated ring, which in addition to the nitrogen atom carrying the groups R^5 and R^6 can also contain one or more further ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, (C_1-C_3)-hydroxyalkyl, -(C_1-C_3)-alkyl-O-(C_1-C_4)-alkyl, aryl, CF_3, OH, -O-(C_1-C_7)-alkyl, -O-aryl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, (C_2-C_3)-alkylenedioxy, NR^8R^9, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N$((C_1-C_3)$-alkyl$)_2$, COOH, CO-O-(C_1-C_5)-alkyl, CHO, CO-(C_1-C_5)-alkyl, $S(O)_n$-(C_1-C_4)-alkyl, $S(O)_n$-NH_2, $S(O)_n$-NH-(C_1-C_3)-alkyl, $S(O)_n$-N$((C_1-C_3)$-alkyl$)_2$, oxo, -$(CH_2)_m$-NH_2, -$(CH_2)_m$-NH-(C_1-C_4)-alkyl and -$(CH_2)_m$-N$((C_1-C_4)$-alkyl$)_2$, where in the substituent -$(CH_2)_m$-N$((C_1-C_4)$-alkyl$)_2$ the two alkyl groups can be linked by a single bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms, can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^7 is OH, -O-(C_1-C_7)-alkyl, NH_2, -NH-(C_1-C_4)-alkyl or -N$((C_1-C_4)$-alkyl$)_2$, where in the substituent N$((C_1-C_4)$-alkyl$)_2$ the two alkyl groups can be linked by a single bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which in addition to the nitrogen atom and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^8 is hydrogen or (C_1-C_7)-alkyl which can be substituted by one or more identical or different substituents from the group consisting of OH, -O-(C_1-C_5)-alkyl, NH_2, -NH-(C_1-C_4)-alkyl and -N$((C_1-C_4)$-alkyl$)_2$, where in the substituent N$((C_1-C_4)$-alkyl$)_2$ the two alkyl groups can be linked by a single bond and then together with the nitrogen atom carrying them form a 5-membered to 7-membered ring which in addition to the nitrogen atom

and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^9, independently of R^8, has one of the meanings of R^8 or is CO-(C_1-C_4)-alkyl;

aryl is phenyl, naphthyl or heteroaryl, which can all be substituted by one or more identical or different substituents from the group consisting of halogen, (C_1-C_5)-alkyl, phenyl, tolyl, CF_3, NO_2, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_3)-alkyl, -N((C_1-C_3)-alkyl)$_2$, NH-CHO, -NH-CO-(C_1-C_5)-alkyl, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_5)-alkyl, $S(O)_n$-(C_1-C_4)-alkyl, $S(O)_n$-phenyl, $S(O)_n$-tolyl, $S(O)_2$-NH_2, $S(O)_2$-NH-(C_1-C_3)-alkyl and $S(O)_2$-N((C_1-C_3)-alkyl)$_2$;

heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle which in each case contain one or more ring heteroatoms from the group consisting of N, O and S;

heterocyclyl is the radical of a monocyclic or polycyclic, 5-membered to 11-membered saturated or partially unsaturated heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, NH_2, -NH-(C_1-C_3)-alkyl, -N((C_1-C_3)-alkyl)$_2$, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH and CO-O-(C_1-C_5)-alkyl;

n is 0, 1 or 2;

m is 2, 3 or 4;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts.

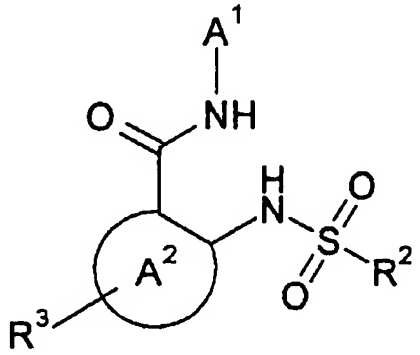
9. A compound of the formulae Ii or Ik as claimed in claim 7 or 8 and/or its physiologically tolerable salts for use as a pharmaceutical.

10. A pharmaceutical preparation which contains one or more compounds of the formulae Ii or Ik as claimed in claim 7 or claim 8 and/or their physiologically tolerable salts in addition to pharmaceutically innocuous vehicles and/or additives.

Abstract

Sulphonylaminocarboxylic acid N-arylamides as guanylate cyclase activators

The present invention relates to compounds of the formula I

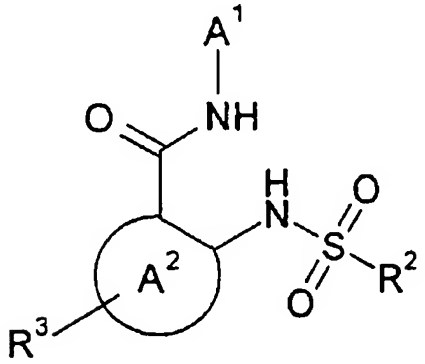


I

in which A^1, A^2, R^2 and R^3 have the meanings indicated in the claims, which are valuable pharmaceutical active compounds for the therapy and prophylaxis of illnesses, for example of cardiovascular disorders such as high blood pressure, angina pectoris, cardiac insufficiency, thromboses or atherosclerosis. The compounds of the formula I have the ability to modulate the endogenous production of cyclic guanosine monophosphate (cGMP) and are generally suitable for the therapy and prophylaxis of disease states which are associated with a disturbed cGMP balance. The invention relates to the use of compounds of the formula I for the therapy and prophylaxis of the designated disease states and for the production of pharmaceuticals therefore, novel compounds of the formula I, pharmaceutical preparations comprising them and processes for their production.

Sulphonylaminocarboxylic acid N-arylamides as guanylate cyclase activators

The present invention relates to compounds of the formula I



I

in which A^1, A^2, R^2 and R^3 have the meanings indicated below, which are valuable pharmaceutical active compounds for the therapy and prophylaxis of diseases, for example of cardiovascular disorders such as high blood pressure, angina pectoris, cardiac insufficiency, thromboses or atherosclerosis. The compounds of the formula I have the ability to modulate the endogenous production of cyclic guanosine monophosphate (cGMP) and are generally suitable for the therapy and prophylaxis of disease states which are associated with a disturbed cGMP balance. The invention relates to the use of compounds of the formula I for the therapy and prophylaxis of the designated disease states and for the production of pharmaceuticals therefore, novel compounds of the formula I, pharmaceutical preparations comprising them and processes for their preparation.

cGMP is an important intracellular messenger, which elicits a number of pharmacological effects by means of the modulation of cGMP-dependent protein kinases, phosphodiesterases and ion channels. Examples are smooth muscle relaxation, the inhibition of platelet activation and the inhibition of smooth muscle cell proliferation and leukocyte adhesion. cGMP is produced by particulate and soluble guanylate cyclases as a response to a number of extracellular and intracellular stimuli. In the case of the particulate guanylate cyclases, the stimulation essentially takes place by means of peptide signal substances, such as the atrial natriuretic

peptide or the cerebral natriuretic peptide. The soluble guanylate cyclases (sGC), which are cytosolic, heterodimeric heme proteins, however, are essentially regulated by a family of low molecular weight, enzymatically formed factors. The most important stimulant is nitrogen monoxide (NO) or a closely relates species. The importance of other factors such as carbon monoxide or the hydroxyl radical is still largely unclarified. The binding of NO to the heme with formation of a pentacoordinated heme-nitrosyl complex is discussed as an activation mechanism of activation by NO. The release associated therewith of the histidine which is bound to the iron in the basal state converts the enzyme into the activated conformation.

Active soluble guanylate cyclases are each composed of one α- and one β-subunit. Several subtypes of the subunits have been described, which differ from one another with respect to sequence, tissue-specific distribution and expression in various stages of development. The subtypes α_1 and β_1 are mainly expressed in the brain and lung, while β_2 is especially found in liver and kidney. The subtype α_2 was detected in human fetal brain. The subunits designated as α_3 and β_3 were isolated from human brain and are homologous to α_1 and β_1. More recent studies point to an α_{2i} subunit, which contains an insert in the catalytic domain. All subunits show great homology in the area of the catalytic domain. The enzymes probably contain one heme per heterodimer, which is bonded via β_1-Cys-78 and/or β_1-His-105 and is part of the regulatory center.

The formation of guanylate cyclase-activating factors can be decreased under pathological conditions or increased degradation thereof can take place as a result of the increased occurrence of free radicals. The decreased activation of the sGC resulting therefrom leads, via the attenuation of the respective cGMP-mediated cell response, for example, to an increase in the blood pressure, to platelet activation or to increased cell proliferation and cell adhesion. As a result, the formation of endothelial dysfunction, atherosclerosis, high blood pressure, stable and unstable angina pectoris, thromboses, myocardial infarct, strokes or erectile dysfunction occurs. The pharmacological stimulation of the sGC offers a possibility for the normalisation of cGMP production and thus allows the treatment or prevention of illnesses of this type.

For the pharmacological stimulation of sGC, until now compounds have almost exclusively been used whose action is based on an intermediate

release of NO, for example organic nitrates. The disadvantage of this method of treatment lies in the development of tolerance and weakening of action and the higher dose which therefore becomes necessary.

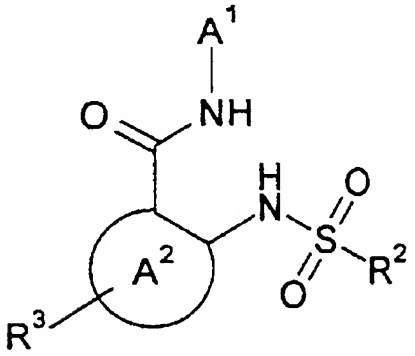
Various sGC stimulators which do not act via a release of NO have been described in a relatively large number of studies by Vesely. The compounds, which are mostly hormones, plant hormones, vitamins or, for example, natural substances such as lizard toxins, however, without exception show only weak effects on cGMP formation in cell lysates (D. L. Vesely, Eur. J. Clin. Invest. 15 (1985) 258; D. L. Vesely, Biochem. Biophys. Res. Comm. 88 (1979) 1244). Stimulation of heme-free guanylate cyclase by protoporphyrin IX was detected by Ignarro et al. (Adv. Pharmacol. 26 (1994) 35). Pettibone et al. (Eur. J. Pharmacol. 116 (1985) 307) describe a hypotensive action for diphenyliodonium hexafluorophosphate and attributed this to a stimulation of sGC. Isoliquiritiginin, which shows a relaxant action on isolated rat aortas, likewise activates sGC according to Yu et al. (Brit. J. Pharmacol. 114 (1995) 1587). Ko et al. (Blood 84 (1994) 4226), Yu et al. (Biochem. J. 306 (1995) 787) and Wu et al. (Brit. J. Pharmacol. 116 (1995) 1973) detected an sGC stimulating activity of 1-benzyl-3-(5-hydroxymethyl-2-furyl)indazole and demonstrated an antiproliferative and platelet-inhibiting action.

A number of sulphonylaminocarboxylic acid N-arylamides of the formula I are already known. Compounds of this type are used, for example, in the production of photographic materials (see, for example, Chemical Abstracts 119, 105 755; 116, 245 151 and 104, 177 628) and, for this purpose, then in general contain in the N-aryl group as substituents easily oxidizable groups such as, for example, two hydroxyl groups in the para-position to one another. For various compounds of the formula I, a pharmacological action has also already been described. Thus, for example, in DE-A-35 23 705, an anthelmintic action is described for a series of 2-phenylsulphonylaminobenzamides. Antiparasitic, antimicrobial or fungicidal actions of 2-sulphonylaminobenzoic acid N-(hetero)arylamides are also mentioned, for example, in EP-A-420 805 and in Chemical Abstracts 122, 136 749; 120, 560; 119, 116 978; 116, 228 237; 116, 207 806; 115, 158 666 and 106, 152 850. According to EP-A-347 168, certain compounds of the formula I having a phenyl pivalate structure are elastase inhibitors and can be used in the treatment of atherosclerosis or arthritis. In Chemical Abstracts 104, 33 896, a psychotropic action is described for

certain 2-sulphonylaminobenzoic acid N-phenoxyphenylamides. Various 2-trifluoromethylsulphonylamino- and 2-methylsulphonylamino-substituted benzamides are described as angiotensin II receptor antagonists having antihypertensive activity in Hypertension 15 (1998) 823, J. Med. Chem. 33 (1990) 1312, EP-A-253 310, EP-A-324 377, EP-A-449 699, EP-A-530 702 and US-A-4 880 804.

Surprisingly, it has now been found that the compounds of the formula I bring about strong guanylate cyclase activation, on account of which they are suitable for the therapy and prophylaxis of illnesses which are associated with a low cGMP level.

The present invention thus relates to the use of compounds of the formula I,



I

in which

A^1 is a radical from the group consisting of phenyl, naphthyl and heteroaryl, which can all be substituted by one or more identical or different radicals R^1;

the ring A^2, which includes the carbon atoms which carry the groups CO-NH- and NH-SO_2R^2, is a benzene ring, a naphthalene ring, a saturated or partially unsaturated 3-membered to 7-membered carbocycle, a saturated, partially unsaturated or aromatic monocyclic 5-membered to 7-membered heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S, or a saturated, partially unsaturated or aromatic bicyclic 8-membered to 10-membered heterocycle, which contains one or more ring heteroatoms from the group consisting of N, O and S;

R^1 is halogen, aryl, CF_3, NO_2, OH, -O-(C_1-C_7)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, -O-aryl, (C_1-C_2)-alkylenedioxy, NR^5R^6, CN, CO-NR^5R^6, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_{10})-alkyl, CO-aryl or (C_1-C_{10})-alkyl, which can be substituted by one or more identical or different radicals R^4;

R^2 is aryl, heterocyclyl, NR^5R^6 or (C_1-C_{10})-alkyl, which can be substituted by one or more identical or different radicals R^4;

R^3 is one or more identical or different substituents from the group consisting of hydrogen, halogen, CF_3, OH, -O-(C_1-C_{10})-alkyl, -O-(C_1-C_7)-alkyl-R^7, -O-aryl, SH, -S-(C_1-C_{10})-alkyl, -S-(C_1-C_7)-alkyl-R^7, -S-aryl, (C_1-C_3)-alkylenedioxy, CN, NO_2, NR^8R^9, CO-NR^5R^6, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, $S(O)_n$-(C_1-C_7)-alkyl, $S(O)_n$-aryl, $S(O)_n$-NR^5R^6 and (C_1-C_7)-alkyl, which can be substituted by one or more identical or different radicals R^4;

R^4 is fluorine, OH, -O-(C_1-C_{10})-alkyl, -O-(C_1-C_7)-alkyl-R^7, -O-aryl, SH, -S-(C_1-C_{10})-alkyl, -S-(C_1-C_7)-alkyl-R^7, -S-aryl, -P(O)(O-(C_1-C_5)-alkyl)$_2$, -P(O)-$(OH)_2$, CN, NR^8R^9, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl or oxo;

R^5 is hydrogen, (C_1-C_{10})-alkyl which can be substituted by one or more identical or different substituents R^4 and/or by aryl, or is aryl, heterocyclyl, CO- (C_1-C_{10})-alkyl, CO-aryl, CO-heterocyclyl, SO_2-(C_1-C_{10})-alkyl, SO_2-aryl or SO_2-heterocyclyl;

R^6, independently of R^5, has one of the meanings indicated for R^5, or R^5 and R^6, together with the nitrogen atom to which they are bonded, form a 5-membered to 8-membered saturated or partially unsaturated ring which, in addition to the nitrogen atom carrying the groups R^5 and R^6, can also contain one or more further ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, (C_1-C_3)-hydroxyalkyl, -(C_1-C_3)-alkyl-O-(C_1-C_4)-alkyl, aryl, CF_3, OH, -O-(C_1-C_7)-alkyl, -O-aryl, -O-(C_2-C_4)-alkyl-O-(C_1-C_7)-alkyl, (C_2-C_3)-alkylenedioxy, NR^8R^9, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-

alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, CHO, CO-(C_1-C_5)-alkyl, S(O)$_n$-(C_1-C_4)-alkyl, S(O)$_n$-NH_2, S(O)$_n$-NH-(C_1-C_3)-alkyl, S(O)$_n$-N((C_1-C_3)-alkyl)$_2$, oxo, -(CH_2)$_m$-NH_2, -(CH_2)$_m$-NH-(C_1-C_4)-alkyl and –(CH_2)$_m$-N((C_1-C_4)-alkyl)$_2$, where in the substituent -(CH_2)$_m$-N((C_1-C_4)-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then, together with the nitrogen atom carrying them, form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms, can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^7 is OH, -O-(C_1-C_7)-alkyl, NH_2, -NH-(C_1-C_4)-alkyl or -N((C_1-C_4)-alkyl)$_2$, where in the substituent N((C_1-C_4)-alkyl)$_2$ the two alkyl groups can be linked by a single bond and then, together with the nitrogen atom carrying them, form a 5-membered to 7-membered ring which, in addition to the nitrogen atom and the carbon atoms can additionally also contain an oxygen atom, a sulphur atom or a group NR^5 as a ring member;

R^8 is hydrogen or (C_1-C_7)-alkyl, which can be substituted by one or more identical or different substituents from the group consisting of OH, -O-(C_1-C_5)-alkyl, NH_2, -NH-(C_1-C_4)-alkyl and –N((C_1-C_4)-alkyl)$_2$;

R^9, independently of R^8, has one of the meanings of R^8 or is CO-(C_1-C_4)-alkyl;

aryl is phenyl, naphthyl or heteroaryl, which can all be substituted by one or more identical or different substituents from the group consisting of halogen, (C_1-C_5)-alkyl, phenyl, tolyl, CF_3, NO_2, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_3)-alkyl, -N((C_1-C_3)-alkyl)$_2$, NH-CHO, -NH-CO-(C_1-C_5)-alkyl, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N((C_1-C_3)-alkyl)$_2$, COOH, CO-O-(C_1-C_5)-alkyl, heterocyclyl, CHO, CO-(C_1-C_5)-alkyl, S(O)$_n$-(C_1-C_4)-alkyl, S(O)$_n$-phenyl, S(O)$_n$-tolyl, S(O)$_2$-NH_2, S(O)$_2$-NH-(C_1-C_3)-alkyl and S(O)$_2$-N((C_1-C_3)-alkyl)$_2$;

heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle, each of which contain one or more ring heteroatoms from the group consisting of N, O and S;

heterocyclyl is the radical of a monocyclic or polycyclic, 5-membered to 11-membered saturated or partially unsaturated heterocycle which contains one or more ring heteroatoms from the group consisting of N, O and S and which can be substituted by one or more identical or different substituents from the group consisting of fluorine, (C_1-C_5)-alkyl, OH, -O-(C_1-C_5)-alkyl, -O-(C_2-C_4)-alkyl-O-(C_1-C_3)-alkyl, NH_2, -NH-(C_1-C_3)-alkyl, -N$((C_1-C_3)$-alkyl$)_2$, CN, CO-NH_2, CO-NH-(C_1-C_3)-alkyl, CO-N$((C_1-C_3)$-alkyl$)_2$, COOH and CO-O-(C_1-C_5)-alkyl;

n is 0, 1 or 2;

m is 2, 3 or 4;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts for the production of a medicament for the activation of soluble guanylate cyclase.

If groups or substituents can occur a number of times in the compounds of the formula I, they can all independently of one another have the indicated meanings and can each be identical or different.

Alkyl radicals can be straight-chain or branched. This also applies if they are contained in other groups, for example in alkoxy groups, alkoxycarbonyl groups or in amino groups, or if they are substituted. Examples of alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, the n-isomers of these radicals, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl. The term alkyl here is expressly also understood as meaning unsaturated alkyl radicals, i.e. alkyl radicals which contain one or more double bonds and/or one or more triple bonds, i.e. alkenyl radicals and alkynyl radicals. Examples of such radicals are the vinyl radical, the 2-propenyl radical (allyl radical), the 2-butenyl radical, the 2-methyl-2-propenyl radical, the ethynyl radical, the 2-propynyl radical (propargyl radical) or the 3-butynyl radical. Furthermore, the term alkyl here is expressly also understood as meaning radicals in which a cyclic system is formed by means of an internal ring closure, the term alkyl thus also includes saturated and partially unsaturated cycloalkyl radicals and cycloalkylalkyl radicals (alkyl substituted by cycloalkyl). Examples of such cycloalkyl radicals are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl,

which all can also be substituted, for example, by one or more identical or different (C_1-C_4)-alkyl radicals, in particular by methyl. Examples of such substituted cycloalkyl radicals are 4-methylcyclohexyl, 4-tert-butylcyclohexyl or 2,3-dimethylcyclopentyl. Furthermore, the term alkyl, if not stated otherwise, here expressly also includes both unsubstituted alkyl radicals and alkyl radicals which are substituted by one or more, for example one, two, three or four, identical or different aryl radicals. The term alkyl here is thus expressly also understood as meaning arylalkyl radicals, for example benzyl radicals, phenylethyl radicals or indanyl radicals.

A saturated or partially unsaturated 3-membered to 7-membered carbocycle representing the ring A^2 can be derived from the monocyclic parent structures cyclopropane, cyclobutane, cyclopentane, cyclohexane or cycloheptane. If the carbocycle is unsaturated, it can contain, for example, a double bond or, in the case of the 5-membered ring, 6-membered ring or 7-membered ring, also two double bonds, which can be isolated or conjugated. Double bonds can be situated in any desired positions with respect to the groups CO-NH- and NH-SO_2-R^2, thus, for example, a double bond can also be situated between the two ring carbon atoms which carry these two groups.

Phenyl radicals, naphthyl radicals and heterocyclic radicals, for example heteroaryl radicals, if not stated otherwise, can be unsubstituted or can carry one or more, for example one, two, three or four, identical or different substituents, which can be situated in any desired positions. If not stated otherwise, the substituents indicated in the definition of the group aryl, for example, can occur in these radicals as substituents. If, in compounds of the formula I, nitro groups are present as substituents, altogether only up to two nitro groups can be present in the molecule. If, for example, phenyl radicals, phenoxy radicals, benzyl radicals or benzyloxy radicals are present in aryl radicals such as, for example, phenyl radicals and/or in heterocyclic radicals as substituents, the benzene ring in these can also in turn be unsubstituted or can be substituted by one or more, for example one, two, three or four, identical or different radicals, for example by radicals from the group consisting of (C_1-C_4)-alkyl, halogen, hydroxyl, (C_1-C_4)-alkoxy, trifluoromethyl, cyano, hydroxycarbonyl, ((C_1-C_4)-alkoxy)carbonyl, aminocarbonyl, nitro, amino, (C_1-C_4)-alkylamino, di-((C_1-C_4)-alkyl)amino and ((C_1-C_4)-alkyl)carbonylamino.

In monosubstituted phenyl radicals, the substituent can be situated in the 2-position, the 3-position or the 4-position, in disubstituted phenyl radicals the substituents can be situated in the 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl radicals, the substituents can be situated in the 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. Tolyl (= methylphenyl) is 2-tolyl, 3-tolyl or 4-tolyl. Naphthyl can be 1-naphthyl or 2-naphthyl. In monosubstituted 1-naphthyl radicals, the substituent can be situated in the 2-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position, in monosubstituted 2-naphthyl radicals in the 1-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position. In higher substituted naphthyl radicals, for example 1-naphthyl radicals or 2-naphthyl radicals which carry two or three substituents, the substituents can also be situated in all possible positions.

Heteroaryl radicals, heterocyclyl radicals, heterocycles representing the ring A^2 and rings which are formed from two groups bonded to a nitrogen atom together with this nitrogen atom, are preferably derived from heterocycles which contain one, two, three or four identical or different ring heteroatoms, particularly preferably from heterocycles which contain one or two or three, in particular one or two, identical or different heteroatoms. If not stated otherwise, the heterocycles can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. They are preferably monocyclic or bicyclic. The rings are preferably 5-membered rings, 6-membered rings or 7-membered rings. Examples of monocyclic and bicyclic heterocyclic systems from which radicals occurring in the compounds of the formula I can be derived are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-dioxole, 1,3-oxazole, 1,2-oxazole, 1,3-thiazole, 1,2-thiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxin, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine, 1,3-thiazepine, indole, benzothiophene, benzofuran, benzothiazole, benzimidazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, thienothiophenes, 1,8-naphthyridine and other naphthyridines, pteridine, or phenothiazine, all in each case in saturated form (perhydro form) or in partially unsaturated form (for example dihydroform and tetrahydro form) or in maximally unsaturated form if the